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## SOME OBSERVATIONS ON CHANGES IN THE MINERAL CONTENT OF PLASMA AND SERUM.

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THESE studies include: (i) an account of the changes in the plasma during the storage of blood; (ii) a comparison of serum obtained from individuals before and after hæmorrhage of varying degree; and (iii) a comparison of serum obtained before and after transfusion with stored blood or serum.

### Alterations in the Potassium, Sodium, Calcium, Magnesium and Chloride Content of the Plasma during the Storage of Blood.

Several detailed accounts of the biochemical changes occurring in the organic constituents of stored blood have been made, including those of Bick;[1] but little work had been done on the changes occurring in the mineral content of the blood until Jeanneney and Servanti[2] drew attention to the rapid rise in the potassium content of the plasma of stored blood. Scudder, Drew, Corcoran and Bull[3] confirmed this and suggested that the high potassium content of stored blood might cause untoward symptoms in man. At this hospital 300 transfusions of stored blood have been given without serious reactions, and the extensive experience of the use of stored blood in other countries lends no support to this possibility.

The present work is concerned with five elements, three of which (sodium, calcium and chloride) are present in greater amounts, and two (potassium and magnesium) in lesser amounts, in the plasma than in the cells. The respective contents of the serum and cells in milligrammes per 100 cubic centimetres, according to Hald and Eisenmann,[4] are: for sodium, 310 and 28; for calcium, 10·4 and 0·4; for chloride, 372 and 115; for potassium, 17·5 and 320; and for magnesium, 1·7 and 5·5.

#### *Methods.*

The methods used for estimations were the following: for potassium, Kramer's method;[5][6] for sodium, Butler and Tuthill's[7] modification of Barber and Kolthoff's method;[8] for calcium, Kramer and Tisdall's method;[9] for magnesium, Denis's method,[10] with the use of Kuttner and Lichenstein's method for phosphate;[11] and for chloride, Van Slyke's method,[12] with the use of Pincussen's[13] modification. Ammonia was never present in stored blood in amount sufficient to cause an error in potassium estimation.

Blood was collected as described by Wood[14] into "Soluvac" flasks of two-pint capacity containing anticoagulant solution. Immediately after collection the blood was shaken, opened aseptically, and specimens 50 cubic centimetres in amount were removed and placed in sterile bottles with well-fitting sterile rubber corks and stored at 2° C. The blood in the small flasks was subjected to treatment identical with that received by the main stock of stored blood. The small bottle was removed from the refrigerator on the afternoon prior to commencement of analysis; the blood was well shaken, filtered through a gauze filter, and allowed to stand at room temperature (about 18° C.) to separate the red cells. This method was adopted in preference to centrifugation, which increases the hæmolysis of stored blood. In view of Scudder, Drew, Corcoran and Bull's[3] statement that the shape of the container influences the changes taking place in stored blood, the smaller bottles had the same proportions as the "Soluvac" flask. Examinations of the blood stored for the same length of time in "Soluvac" flasks and in sample bottles gave identical values for the potassium in the plasma.

Several samples were necessary, because repeated shaking of blood at short intervals prior to the removal of specimens for analysis is not in accordance with the normal treatment of stored blood, which is neither moved nor shaken from the time of collection until immediately before use, when it is shaken and warmed to body temperature. A specimen of whole blood was obtained by venepuncture prior to the collection of the pint of blood kept for storage. The serum was separated as quickly as possible and the figures from

the analysis of this serum were used as the basis of calculation of the original amounts present in the plasma.

Four anticoagulant solutions were used, all of pH 7·3:

(i) Citrate saline solution of Harrington and Miles[15] (1·05% sodium citrate solution, 0·90% sodium chloride solution).

(ii) Glucose citrate solution of Duran-Jorda[16] ("Solution A" 4·0% sodium citrate, "Solution B" 4·0% sodium citrate and 2·0% glucose). Of "Solution A", 30 cubic centimetres are placed in the flask before collection and 600 cubic centimetres of blood are added, followed by 30 cubic centimetres of "Solution B".

(iii) "New citrate saline" solution of Manzells and Whittaker[17] (1·05% sodium citrate, 0·43% sodium chloride).

(iv) "Dextrin" solution of Manzells and Whittaker (1·05% sodium citrate, 0·43% sodium chloride and 8·50% dextrin). The use of dextrin to preserve red cells was suggested by Rous and Turner[18] as early as 1916. Of solutions (i), (iii) and (iv), 300 cubic centimetres are used with 600 cubic centimetres of blood. The results of analysis of these solutions by the methods described above were used for the calculations in Table I.

### *Results of Investigations.*

The changes in potassium, sodium, calcium and magnesium content of plasma during storage are illustrated by the typical set of observations recorded in Table I.

The blood of Donor I was collected and equal portions were added to the anticoagulant solutions (i) and (iii). Aliquot parts of the blood were placed in the small flasks and analysed seven hours after collection and then at intervals of some days. The same procedure was followed with the blood of Donor II, the blood in this case being stored in solutions (ii) and (iv).

These results confirm the rapid rise in the potassium content of the plasma which takes place as soon as the blood is placed in the anticoagulant solution. In solution (i) there was a rise of 43% at the end of seven hours, and at the end of twenty days the plasma contained 363 milligrammes per 100 cubic centimetres; this was equivalent to an increase of 1,300%. In solution (ii) the increase was 74% at the end of seven hours and 305% at the end of twenty days. In solution (iii) an increase of 71% was obtained in seven hours; rising to 860% at the end of the experiment. In solution (iv), though the increase in seven hours was much less (10%), at the end of twenty days it was 520%. In another experiment the rise was over 92% at the end of one hour. The alteration in the potassium content of the plasma takes place long before the onset of hæmolysis. It is noticeable that solution (ii) (glucose citrate solution), in which only 60 cubic centimetres of anticoagulant solution were added to one pint of blood, caused the least rapid change in the potassium content; it would appear, therefore, that dilution of the blood is one of the factors causing the alteration. Scudder, Drew, Corcoran and Bull's[3] work confirms this view.

Table I.

*Changes in Mineral Contents of the Plasma of Stored Blood.*

| Time After Collection. | Basic Values for Serum. (Milligrammes per 100 Cubic Centimetres.) | | | | | | Plasma *plus* Anticoagulant Solution. (Milligrammes per 100 Cubic Centimetres.) | | | | | | Plasma Calculated in Milligrammes per 100 Cubic Centimetres. | | | | | | Alterations in Mineral Contents in Plasma. (Percentages.) | | | | | | Degree of Hæmolysis. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Potassium. | Sodium. | Calcium. | Magnesium. | Chloride. | | Potassium. | Sodium. | Calcium. | Magnesium. | Chloride. | | Potassium. | Sodium. | Calcium. | Magnesium. | Chloride. | | Potassium. | Sodium. | Calcium. | Magnesium. | Chloride. | | |
| **Blood Stored in Solution (i) (Citrate Saline Solution).** | | | | | | | | | | | | | | | | | | | | | | | | | |
| 1 hour | 26·0 | 324 | 11·0 | 2·7 | 380 | | 19·6 | 448 | 7·5 | 1·61 | 447 | | 37·2 | 285 | 14·2 | 3·01 | 393 | | +43 | −12 | +29 | +12 | +4 | | Nil. |
| 7 hours | | | | | | | 53·4 | 409 | 6·4 | 1·69 | 436 | | 102·0 | 211 | 12·2 | 3·59 | 372 | | +292 | −35 | +11 | +33 | −2 | | Nil. |
| 7 days | | | | | | | 81·0 | 383 | 6·8 | 1·4 | 414 | | 154·0 | 102 | 12·9 | 2·96 | 331 | | +500 | −50 | +17 | +9·6 | −13 | | Moderate. |
| 13 days | | | | | | | 191·0 | 375 | 9·6 | 1·92 | 402 | | 363·0 | 146 | 18·3 | 3·65 | 308 | | +1300 | −55 | +66 | +35 | −19 | | Moderate. |
| **Blood Stored in Solution (ii) (Glucose Citrate Solution).** | | | | | | | | | | | | | | | | | | | | | | | | | |
| 1 hour | 26·4 | 356 | 10·6 | 2·1 | 381 | | 38·9 | 429 | 9·2 | 1·67 | 323 | | 45·9 | 345 | 10·9 | 1·97 | 381 | | +74 | −3·6 | +3 | +6·2 | +0 | | Nil. |
| 7 hours | | | | | | | 61·0 | 375 | 9·0 | 2·1 | 321 | | 102·0 | 281 | 10·6 | 2·48 | 379 | | +173 | −21 | +0 | +18 | +0·5 | | Nil. |
| 7 days | | | | | | | 60·0 | 368 | 9·8 | 1·8 | 312 | | 71·0 | 273 | 11·6 | 2·12 | 368 | | +170 | −27 | +8·6 | +1·0 | −3·4 | | Slight. |
| 13 days | | | | | | | 91·0 | 337 | 11·5 | 2·27 | 298 | | 107·0 | 230 | 13·4 | 2·68 | 352 | | +305 | −34 | +21 | +21 | −8 | | Moderate. |
| **Blood Stored in Solution (iii) (New Citrate Saline Solution).** | | | | | | | | | | | | | | | | | | | | | | | | | |
| 1 hour | 26·0 | 324 | 11·0 | 2·7 | 380 | | 24·5 | 399 | 7·5 | 1·72 | 352 | | 44·5 | 367 | 13·4 | 3·0 | 335 | | +71 | −13 | +22 | +11 | −11 | | Nil. |
| 7 hours | | | | | | | 78·0 | 394 | 7·5 | 2·46 | 368 | | 135·0 | 358 | 13·4 | 4·36 | 363 | | +420 | −10 | +22 | +62 | −5 | | Nil. |
| 7 days | | | | | | | 97·4 | 356 | 7·8 | 1·47 | 358 | | 172·0 | 283 | 13·9 | 2·67 | 345 | | +565 | −12 | +26 | −1 | −9 | | Moderate. |
| 20 days | | | | | | | 287·0 | 337 | 8·5 | 2·05 | 327 | | 510·0 | 256 | 15·1 | 3·65 | 290 | | +860 | −21 | +37 | +39 | −24 | | Moderate. |
| **Blood Stored in Solution (iv) (containing Dextrin).** | | | | | | | | | | | | | | | | | | | | | | | | | |
| 1 hour | 26·4 | 358 | 10·6 | 2·1 | 381 | | 16·1 | 382 | 6·2 | 1·25 | 325 | | 29·0 | 346 | 4·0 | 1·05 | 378 | | +10 | −3·4 | −24 | −51 | −15 | | Nil. |
| 7 hours | | | | | | | 47·0 | 362 | 9·6 | 1·92 | 312 | | 84·6 | 310 | 10·1 | 2·24 | 355 | | +224 | −13 | −5 | +7 | −18 | | Nil. |
| 7 days | | | | | | | 85·6 | 344 | 12·0 | 1·25 | 312 | | 154·0 | 277 | 14·0 | 1·03 | 355 | | +483 | −23 | +31 | −51 | −18 | | Slight. |
| 20 days | | | | | | | 91·0 | 314 | 13·0 | 1·85 | 297 | | 164·0 | 223 | 16·2 | 2·11 | 328 | | +520 | −38 | +53 | +0·5 | −22 | | Moderate. |

These workers found that blood in which clotting was prevented by the addition of solid heparin showed less alteration than that diluted by saline anticoagulants. The total amount of potassium in the plasma given in a pint of blood mixed with anticoagulant solution may, after three weeks' storage, be 2,000 milligrammes or more, as compared with 120 milligrammes, which is the normal potassium content of the plasma of a pint of fresh human blood.

In all four solutions there was a fall in the sodium content of the plasma during storage; this was greatest in solution (i) and least in solution (iii). The fall commenced as soon as the blood was mixed with the anticoagulant solution. It reached 12% in seven hours when the blood was preserved in solution (i), and in other specimens examined it was of the order of 10% at the end of four hours. The fall was independent of the onset of hæmolysis.

The changes in the calcium content of the plasma of the stored blood were irregular. This is illustrated in the four examples given. In the blood preserved in three of the anticoagulant solutions—solutions (i), (ii) and (iii)—there was a steady increase in the calcium content of the plasma; in that preserved in solution (iv) there was a preliminary fall followed by a rise at the end of thirteen days. These results are typical of the irregularities found in the stored blood from twelve donors, and they agree with the findings of several observers, including Waelsch,[19] who found that both sodium and calcium were taken into or onto the red blood cells during the first few hours after collection of blood and that this transference proceeded irregularly. It is possible that the rise in plasma calcium content may be due to portion of the calcium being linked with protein, as suggested by Myers and Muntwyler,[20] and that this linkage breaks down as the time of storage lengthens, increasing the amount of calcium precipitable as oxalate.

Magnesium was estimated in the plasma of only the two donors referred to in Table I, and the changes observed were also irregular. Waelsch reports a rise in the magnesium content of the plasma after blood is shed.

In the blood preserved in all four solutions there was a fall in the chloride content of the plasma; this fall was least in the blood preserved in solution (ii). Solution (ii) is the only one of the four anticoagulant solutions which does not contain chloride. Normally the chloride content of the plasma is twice as great as that of the red blood cells, and if this difference is increased by added chloride, diffusion into the red cells is more rapid. A few isolated estimations of the carbon dioxide combining power were made, but the small fall observed appeared to be insufficient to cause diffusion of chloride from the cells to the plasma in accordance with the Gibbs-Donnan law.[21]

Hæmolysis was slightly less in the blood preserved in solutions (ii) and (iv). On examination of a bottle of blood preserved in solution (iv), which contains dextrin, no zone of hæmolysis was apparent above the red cells at the end of twenty days; but when the blood was shaken and allowed to stand overnight, there was just as much hæmolysis as in solution (ii). Diffusion of hæmoglobin in the plasma after liberation from the red blood cells is apparently slower in this solution than in the others. It would appear that solutions (ii) and (iv) have some advantage over solutions (i) and (iii) in this respect, since there was only very slight hæmolysis at the end of thirteen days.

The changes in the mineral content of the plasma justify the view that during storage the stroma of the red cells ceases to be semi-permeable and allows diffusion to take place between cells and plasma. Equilibrium is not usually reached before hæmolysis occurs. The possible significance of the rise in potassium and fall in sodium in the plasma is discussed later.

### The Potassium, Sodium, Calcium, Magnesium and Chloride Content of the Serum after Hæmorrhage.

There is considerable divergence of opinion concerning the effect of hæmorrhage on the potassium content of the plasma. Scudder, Drew, Corcoran and Bull, who accept the view that the potassium content of the plasma is raised after hæmorrhage, consider, therefore, that the use of stored blood is contraindicated in cases of hæmorrhage.

Schmitt and Basse[22] appear to be the only observers who have attempted to ascertain whether, in man, there is any change in the distribution of potassium, sodium, calcium and magnesium in the blood after hæmorrhage. Two hundred to five hundred cubic centimetres of blood were taken from a vein of normal adults. Changes in the mineral content of the plasma and cells were noted at hourly intervals for four hours and at the end of twenty-four hours. There was a small increase in the potassium, sodium, calcium and chloride content of the plasma; in the red cells a fall occurred in potassium, sodium and chloride content, and a rise in calcium content. This rise of calcium content in both plasma and red cells persisted for twenty-four hours. Kerr[23] found that, in dogs, after a single hæmorrhage, a small fall occurred in the sodium and chloride content of the plasma, the potassium remaining unchanged. Repeated hæmorrhage during four days (the animal was bled to an amount equal to the original blood volume) resulted in a fall in sodium and chloride content of the plasma, the potassium content again remaining normal. Zwemmer and Scudder[24] found that fatal shock in cats produced a rise in the potassium content of the plasma to 50% or 100%. In view of these divergent findings it was thought that further investigation of the results of hæmorrhage in man would be of value.

Two types of hæmorrhage have been studied: (*a*) loss of one pint of blood by venepuncture in healthy subjects, and (*b*) hæmorrhage occurring as a result of disease or accident.

As it was obviously impossible to obtain blood from patients suffering from hæmatemesis or hæmorrhage due to accident prior to their admission to hospital, the serum of 23 normal adults was examined to establish values for comparison. Blood was collected from 13 men and 10 women after a fat-free breakfast. The serum was separated as rapidly as possible from the clot and centrifuged. The results of the analysis are shown in Table II.

Table II.
*Mineral Content of Normal Human Serum.*

| Mineral. | Minimum. (Milligrammes per 100 Cubic Centimetres.) | Maximum. (Milligrammes per 100 Cubic Centimetres.) | Average. (Milligrammes per 100 Cubic Centimetres.) |
|---|---|---|---|
| Potassium .. | 15·6 | 26·5 | 20·5 |
| Sodium .. .. | 316·0 | 358·0 | 336·0 |
| Calcium .. .. | 9·2 | 11·5 | 10·2 |
| Magnesium .. | 1·95 | 2·79 | 2·32 |
| Chloride .. .. | 329·0 | 381·0 | 363·0 |

#### *The Effect of Moderate Hæmorrhage.*

Blood was collected by venesection from 16 healthy adults after a fat-free breakfast; one pint of blood was obtained in the course of ten to twenty minutes. Before and after venesection 10 cubic centimetre samples of blood were removed from a vein. The serum from these samples was obtained rapidly and subjected to analysis. The results of analysis of the serum from two subjects shown in Table III are typical; no significant change was demonstrated in any of the mineral constituents.

#### *The Effect of Severe Hæmorrhage.*

Serum was obtained from 11 patients after severe hæmorrhage and from one after a moderate hæmorrhage. The results of analysis of the serum are set out in Table IV.

The average values found for potassium, sodium, calcium and magnesium in the serum of these patients was in agreement with those found in normal adults. In Case IX the potassium content of the serum was one milligramme higher than the maximum found in the normal series, and in Cases IV and V the magnesium content of the serum exceeded that found in the normal series; but these differences cannot be regarded as significant.

TABLE III.

*The Potassium, Sodium, Calcium, Magnesium and Chloride Content of the Serum Before and After Removal of One Pint of Blood by Venepuncture.*

| Case. | Time. | Potassium. (Milligrammes per 100 Cubic Centimetres.) | Sodium. (Milligrammes per 100 Cubic Centimetres.) | Calcium. (Milligrammes per 100 Cubic Centimetres.) | Magnesium. (Milligrammes per 100 Cubic Centimetres.) | Chloride. (Milligrammes per 100 Cubic Centimetres.) |
|---|---|---|---|---|---|---|
| I | Before removal of blood | 17·2 | 329 | 11·4 | 1·92 | 363 |
| | After removal of blood | 18·1 | 331 | 11·4 | 2·00 | 369 |
| II | Before removal of blood | 22·4 | 329 | 10·9 | 2·00 | 369 |
| | After removal of blood | 18·5 | 326 | 11·0 | 2·00 | 369 |

TABLE IV.

*Potassium, Sodium, Calcium and Magnesium Content of the Serum after Severe Hæmorrhage in Milligrammes per 100 Cubic Centimetres.*

| Case. | Pathological Condition. | Estimated Loss of Blood. | Potassium. | Sodium. | Calcium. | Magnesium. |
|---|---|---|---|---|---|---|
| I | Menorrhagia | Considerable. | 21·6 | — | 9·2 | — |
| II | Bleeding uterine fibroid | Considerable. | 18·5 | 342 | 9·2 | — |
| III | Hæmatemesis | More than three pints in three days. | 22·8 | — | 7·1 | 2·8 |
| IV | Hæmatemesis | Three pints in 48 hours. | 20·0 | 381 | 12·4 | 3·2 |
| V | Hæmatemesis | Two pints in 48 hours. | 20·2 | 336 | 10·6 | 3·1 |
| VI | Hæmatemesis | Four pints in 14 hours. | 25·0 | 329 | 9·6 | 2·1 |
| VII | Hæmatemesis | Severe loss. | 23·0 | 327 | 10·9 | 1·8 |
| VIII | Polycythæmia | Half a pint vomited. | 17·6 | 349 | 11·2 | 2·0 |
| IX | Hæmatemesis | Eight pints in week. | 27·7 | 331 | 10·0 | 1·8 |
| X | Hæmatemesis | Four pints in two days. | 19·7 | 229 | 11·5 | 2·6 |
| XI | Hæmatemesis | Three pints in 24 hours. | 21·9 | 291 | — | — |
| XII | Hæmatemesis | Chronic bleeding. | 19·1 | — | 8·2 | 2·4 |
| Average of cases of hæmorrhage | | | 21·4 | 324 | 10·0 | 2·4 |
| Average of normal cases | | | 20·5 | 336 | 10·2 | 2·3 |

### Chemical Changes in the Serum after Transfusion of Stored Blood or Serum.

The toxic effect of potassium injected intravenously into animals has been known for nearly a century[28] and has been experimentally confirmed by many observers. Scudder, Drew, Corcoran and Bull[3] found, in rabbits, that 32 milligrammes per kilogram of body weight, injected rapidly into a vein, were a fatal dose, and that in dogs 62 milligrammes per kilogram of body weight injected intravenously during three minutes caused a rise in the plasma potassium content of from 19 milligrammes to 99 milligrammes per 100 cubic centimetres at death, which took place a few minutes after injection. The detoxifying action of sodium has been noted by many observers, including Amberg and Helmholz,[29] who found that a preliminary injection of 5% sodium chloride solution would protect an animal against an otherwise fatal dose of potassium chloride, and that 50% glucose solution also had a protective effect. It has been assumed that excess potassium would have a similar effect in man.

In Table V are shown the effects of the intravenous injection of stored blood (in three cases) and of stored serum (in eight cases) on the mineral content of the serum. In the three cases in which stored blood was given there was no significant change in any of the constituents studied. It may be noted, however, that only in Case III was the dose given of a size (8·5 milligrammes per kilogram) which might be expected to raise the potassium content of the recipient's serum.

Eight patients were given transfusions of stored pooled human serum. This serum was prepared at the Commonwealth Serum Laboratories by the method of Morgan.[27] The serum was stored either in the refrigerator or at room temperature. The rather erratic values for calcium found in the pooled serum are due to the method of collection and preparation; the procedure was, first, admixture with potassium oxalate and, subsequently, precipitation of the oxalate with calcium chloride to allow clotting. This procedure probably accounts in part for the consistently high values for potassium found in the various samples of this serum which were examined. In none of these eight cases was there any significant change in the potassium content of the serum, though there were obvious alterations in the level of sodium, calcium and chloride. In Case VI, for example, two pints of serum were given by transfusion in eight hours. The total amount of potassium given to the patient was 1,388 milligrammes, which is equivalent to almost 20 milligrammes per kilogram of body weight for a patient weighing 70 kilograms. If it is assumed, following Rowntree and Brown,[26] that the plasma volume per kilogram of body weight is 50 cubic centimetres, this amount of potassium should be sufficient to raise the serum potassium by 40 milligrammes per 100 cubic centimetres if it was distributed only in the plasma, or by 14 milligrammes per 100 cubic centimetres if it was distributed throughout the body fluid. The serum potassium content was, however, unchanged at the end of the transfusion. The sodium content of the transfused serum averaged 289 milligrammes per 100 cubic centimetres for the two pints, and this administration of fluid of low sodium content caused a fall in the patient's serum sodium level from 478 milligrammes per 100 cubic centimetres before transfusion to 400 milligrammes per 100 cubic centimetres after transfusion. The serum protein level rose from 5·5 grammes per 100 cubic centimetres to 6·0 grammes per 100 cubic centimetres after transfusion.

These eleven cases illustrate the fact that in man serum or blood with a high potassium content, given at the rate of one pint per hour, causes no ill effects nor any significant change in the serum potassium level of the recipient. On the other hand, differences between the concentration of the sodium and calcium in the transfused fluid and that in the recipient's blood before transfusion are sometimes reflected in a corresponding alteration in the amounts of these substances found in the recipient's serum after transfusion.

In view of the detoxifying influence of sodium on potassium, which has been demonstrated in animals by Amberg and Helmholz,[29] it has been suggested that the absence of toxic effects, which a high potassium content in stored blood might be expected to produce in human recipients, could be explained by the fact that, owing to the addition of sodium citrate and sodium chloride to such blood before storage, it contains a much higher concentration of sodium than is normally present in fresh blood. It has been shown, however, in the first part of this paper, that the sodium content of stored plasma, though initially high, falls during storage, the sodium ion presumably penetrating the red cells, so that in the plasma-anticoagulant mixture there are during storage a rising potassium and falling sodium content.

TABLE V.

*Potassium, Sodium, Calcium, Magnesium and Chloride Content of Recipient's Serum Before and After Transfusion of (a) Stored Blood, and (b) Stored Serum.*

| Case. | Anti-coagulant Solution Used. | Amount Given. | Time Stored. | Rate of Transfusion. | Mineral Content of Blood and Solution (or Stored Serum) given by Transfusion. (Milligrammes per 100 Cubic Centimetres.) | | | | | Total Amount of Minerals Given. (Milligrammes.) | | | | | Mineral Content of Recipient's Serum Before Transfusion. (Milligrammes per 100 Cubic Centimetres.) | | | | | Mineral Content of Recipient's Serum After Transfusion. (Milligrammes per 100 Cubic Centimetres.) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Potassium. | Sodium. | Calcium. | Magnesium. | Chloride. | Potassium. | Sodium. | Calcium. | Magnesium. | Chloride. | Potassium. | Sodium. | Calcium. | Magnesium. | Chloride. | Potassium. | Sodium. | Calcium. | Magnesium. | Chloride. |
| | | | | | | | | | | *Stored Blood.* | | | | | | | | | | | | | |
| I | (a) | 1 pint. | 1 day. | 7 hours. | 58·5 | 440 | 9·2 | 2·38 | 318 | 210 | 1584 | 33·0 | 8·63 | 1205 | 18·5 | 342 | 9·2 | 2·50 | 347 | 20·8 | 332 | 9·2 | 2·94 | 350 |
| II | (c) | 1 pint. | 1 day. | 7 hours. | 27·7 | 496 | 4·2 | 1·05 | 465 | 249 | 4464 | 37·0 | 9·45 | 4185 | — | — | — | — | — | — | — | — | — | — |
| III | (a) | 1 pint. | 2 days. | 4 hours. | 52·5 | 360 | 9·6 | 2·50 | 315 | 189 | 1296 | 35·0 | 9·00 | 1134 | 25·2 | 303 | 11·5 | 3·2 | 355 | 24·8 | 288 | 11·5 | 2·2 | 334 |
| | (b) | 1 pint. | 3 days. | 6 hours. | 70·0 | — | 11·2 | — | 312 | 252 | — | 40·0 | — | 1123 | 21·6 | — | 9·2 | — | 312 | 23·1 | — | 9·8 | — | 327 |
| | (d) | 1 pint. | 3 days. | 6 hours. | 102·4 | — | 7·4 | — | 301 | 360 | — | 27·0 | — | 3249 | — | — | — | — | — | — | — | — | — | — |
| | | | | | | | | | | *Stored Serum.* | | | | | | | | | | | | | |
| IV | | 1 pint.[1] | 2 months. | 1 hour. | 93·1 | 254 | 3·1 | — | 558 | 1524 | 18·6 | — | 1205 | 22·0 | 10·8 | — | — | 1968 | 23·3 | 9·3 | — | — | — |
| V | | 1 pint.[1] | 2½ months. | 2 hours. | 94·0 | 258 | 9·2 | 3·30 | 564 | 1548 | 55·2 | 19·8 | 4185 | 22·8 | 7·1 | 478 | 2·85 | 2280 | 22·4 | 8·2 | 400 | 2·70 | — | — |
| VI | | 2 pints.[1] | 3 months. | 4 hours. | 117·0 | 306 | — | — | 704 | 1836 | — | — | 1134 | 20·5 | — | — | — | 336 | 20·0 | — | — | — | — | — |
| VII | | 1 pint.[2] | 5 months. | 4 hours. | 114·0 | 272 | — | — | 684 | 1632 | — | — | 1123 | — | — | — | — | — | — | — | — | — | — | — |
| VIII | | 1 pint.[2] | 5 months. | 1 hour. | 105·0 | 250 | 9·8 | 3·0 | 630 | 1500 | 58·8 | 18·0 | — | 26·0 | 10·8 | 302 | 11·0 | — | — | 25·0 | 292 | 10·8 | 2·2 | — |
| IX | | 1 pint.[2] | 5 months. | 1 hour. | 105·0 | 250 | 9·8 | 3·0 | 630 | 1500 | 58·8 | 18·0 | — | 26·0 | 21·2 | 302 | 11·0 | 3·1 | — | 20·8 | 287 | 10·6 | 3·1 | — |
| X | | 1 pint.[1] | 5 months. | 4 hours. | 105·0 | 250 | 9·7 | — | 630 | 1500 | 58·8 | — | — | 18·4 | 10·2 | 286 | 10·2 | 2·4 | 336 | 19·0 | 280 | 10·2 | 2·7 | 332 |
| XI | | 1 pint.[2] | — | 1½ hours. | 43·3 | — | 8·2 | — | 325 | 612 | — | — | — | 19·1 | 8·2 | — | — | — | 336 | 19·8 | — | 9·0 | — | 365 |
| | | | | | | | | | 380 | 260 | | | | 23·9 | 10·4 | | | | | 22·5 | | 9·8 | | |

[1] Stored in refrigerator. [2] Stored at room temperature. [3] Dried serum redissolved in water.

Amberg and Helmholz did not give figures for the molar sodium to molar potassium ratio in their experiments; but from their dosage of sodium chloride and potassium chloride the minimum ratio they found necessary to prevent the animal from succumbing to injected potassium was between 2·6 : 1 and 4 : 1. This ratio is at 22 : 1 in normal freshly shed blood, and as storage proceeds there is an alteration in the relationship of molar sodium to molar potassium. For example, in solution (i) the ratio is 40 : 1 seven hours after the blood has been placed in the anticoagulant solution, 13 : 1 after seven days' storage, 8 : 1 after thirteen days, and 3 : 1 after twenty days. In solution (ii) the ratio is 7 : 1, in solution (iii) it is 2 :1, and in solution (iv) it is 6 : 1 after twenty days' storage. The preliminary rise to 40 : 1 is due to the large amount of sodium present as chloride or citrate in the anti-coagulant solution. If Helmholz's protective dosage of sodium is correct, it may be inadvisable to extend the period of storage beyond two weeks. The molar relationship between the sodium and potassium in the stored blood or serum used for transfusion in the cases shown in Table V was as follows: in Case I, 17 : 1; in Case II, 12 : 1; in Cases IV and V, 5 : 1; and in Cases VI to IX, 4 : 1.

The relationship of the lethal dose to the rate at which the injected potassium is given to animals has been studied by Houssay and Mareynz,[20] Scudder, Drew, Corcoran and Bull,[3] and Wilde.[30] These workers observed that with slower administration ill effects were less evident. In the series of 11 cases described in Table V, the most rapid rate of administration was one pint of serum per hour, containing 630 milligrammes of potassium. The slow rate of administration in man probably minimizes possible ill effects.

## Summary.

1. In confirmation of the conclusions of other workers, the potassium content of the plasma was observed to increase during storage. The increase commences as soon as the shed blood is mixed with the anticoagulant solution. The chloride and sodium content of the plasma decreases, while calcium and magnesium content increases somewhat irregularly.

2. These changes are minimal in the glucose-citrate anti-coagulant solution of Duran-Jorda.

3. No significant changes were observed in the mineral constituents of the serum obtained after hæmorrhage.

4. The administration of large amounts of potassium in transfusions of stored blood or serum does not cause any significant rise in the potassium content of the serum obtained from the recipient after this treatment. This may be attributed to dilution of the tissue fluids as well as by the plasma of the recipient.

5. The absence of toxic effects after these large doses of potassium is attributed to the presence in sufficient amounts of neutralizing sodium ions in the stored blood or serum and to the slow rate of transfusion.

## Acknowledgements.

My thanks are especially due to Dr. R. Jakobowicz, who helped with many of the analyses, and to Miss F. E. Williams, for the provision of stored blood from the blood bank.

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## THE EFFECT OF TESTOSTERONE PROPIONATE ON POUCH, SCROTUM, CLITORIS AND PENIS OF TRICHOSURUS VULPECULA.

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IN connexion with our work on the action of sex hormones on marsupials we injected the male sex hormone testosterone propionate into a series of male and female phalangers or possums (*Trichosurus vulpecula*) of varying ages. Following these injections certain modifications in the sex organs were observed which will be detailed in the following description of our experiments. On this occasion, however, we shall principally describe the macroscopic changes observed in the intact animal. They were alterations in the pouch, in the scrotum and in the cloacal region.

### Administration of Testosterone Propionate to Females.

The females used in this study were: (*a*) two pouch young, aged about three months; (*b*) two immature females, aged respectively eight and nine months; and (*c*) one fully grown sexually mature specimen. These animals were injected intramuscularly with testosterone propionate dissolved in sesame oil ("Perandren", Ciba). In the case of the pouch young which were still attached to the nipple of the mother, the mother was slightly anæsthetized and the hind end of the young was lifted out of the relaxed pouch for the injection of testosterone propionate.

#### *Changes in and around the Pouch.*

The structure of the pouch has already been described in a previous article, and its response to other sex hormones, such as œstrogens and progesterone, has been reported elsewhere.[1][2] In addition to the earlier reported observations about the colour of the hairs in the region of the lower portion of the abdomen, and particularly around the pouch, it has to be mentioned that the first hairs which grow on the pouch embryo in that region are usually colourless for a short period of a few weeks. Then, in the female as well as in the male, they change towards a golden yellow over nearly the entire ventral area, while the claws also become a deep yellow colour. This golden yellow coloration of the ventral hairs of young possums about to leave the pouch has been recorded by Wood Jones.[3] The now numerous ventral hairs rapidly turn white as soon as the young becomes independent of its mother, and the claws also lose their deep yellow colour. This observation on animals kept in captivity confirms an earlier statement with regard to females, according to which specimens of six months of age or somewhat older obtained directly from the bush have practically pure white hairs on their abdomen.[4]

(*a*) *Pouch Young.*—Two pouch young, aged about three months, which were still in the hairless stage, were given weekly injections of five milligrammes of testosterone propionate. In the pre-experimental stage the pouch area was enclosed by two ridges which met caudally in a V-shaped or U-shaped manner, while two small nipples were observed near the posterior end of this area. Within a few days after the first injection the pouch of these young animals registered a response. The lips became thickened and approximated to each other. The mammæ, which were hardly noticed before the experiment was started, increased greatly in size, in such a manner that two bulges of about two millimetres in maximum height appeared beneath the lips. Within the next few weeks the lips further increased in thickness and they also became puckered, as if they were contracted (Figure I). On the enlarged nipples the typical yellow-brown secretion which had been observed on previous occasions[1][4] was noted. For the next two months the lips remained in a very thickened state, but later on this became less conspicuous. In one of the two specimens injections were continued for eight months without variation in the dosage. After the experiment had been going on for five months the pouch was found to be of approximately normal size as compared with controls. The lips, however, were still slightly thickened, but the puckering had completely disappeared. After eight months the pouch was definitely smaller than in controls of similar age.

(*b*) *Immature Females.*—The smaller of the two immature females (body weight, 0·8 kilogram) received weekly injections of 10 milligrammes of testosterone propionate; the larger one (body weight, 1·3 kilograms) received weekly injections of 50 milligrammes. In many

respects the findings in both of these instances were similar to those observed in the pouch young. After a few injections the lips of the pouch became thickened and the mammæ became hypertrophied; but in addition a clear white fluid was secreted from the nipples over a period of several weeks. Later on, the nipples became capped with the orange-brown pigment mentioned before. In the case of the younger animal, injections were continued for six and a half months. At the end of the experiment the pouch was found to be of subnormal dimensions, being in an atrophic state as compared with that of controls of similar age. At this stage a huge abdominal tumour developed, which on post-mortem examination proved to be a grossly enlarged median vagina.

(*c*) *Sexually Mature Female.*—Fifteen milligrammes of testosterone propionate were injected weekly into a sexually mature female for a period of six weeks. The pouch of this animal did not show any typical changes.

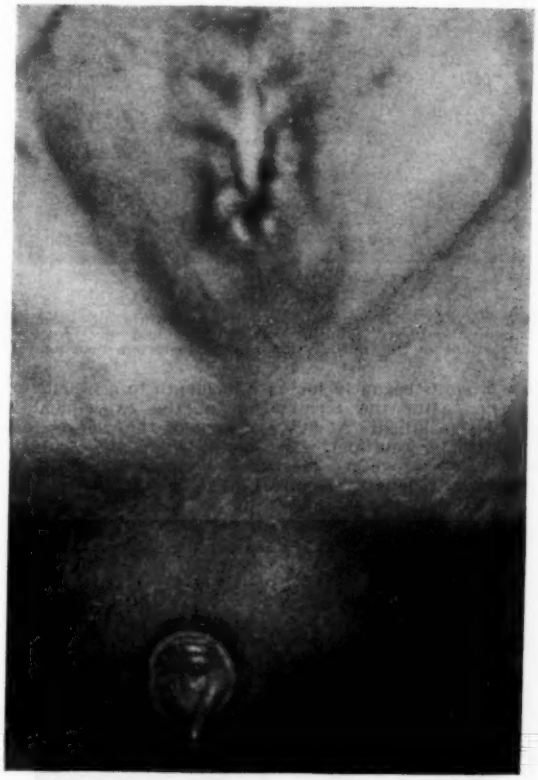

FIGURE I.

Group (*a*). Female, aged about five months, after six weekly injections of five milligrammes of testosterone propionate. The photograph shows the swollen and puckered lips of the pouch, hypertrophic cloacal hillock and large protruding clitoris. Note the flagellum on the clitoris.

### *Changes in the Clitoris.*

*Trichosurus vulpecula*, in common with most marsupials, possesses at the caudal end of the body, in front of the root of the tail, a conical elevation of moderate height, the so-called cloacal hillock, consisting *inter alia* of bulbo-vestibular glands and *corpora cavernosa*. This carries on its end the external opening of the cloaca. In the female the cloaca consists of the rectal canal, into which merges the uro-genital canal. Beneath the opening of the urogenital canal is situated the clitoris, which is partly covered by a preputial skin. In fully grown animals the clitoris is small and measures about three to six millimetres in length and one to two millimetres in diameter. On its dorsal surface it contains a narrow longitudinal groove and has a tiny flagellum at its caudal end. At no stage of development was the clitoris seen to protrude from the cloacal opening.

The same animals as have already been mentioned in connexion with changes in the pouch will be described now with regard to changes in the clitoris.

(*a*) *Pouch Young.*—In the two pouch young which received five milligrammes of testosterone propionate per week, enlargement of the cloacal hillock (mainly due to increase in size of the bulbo-vestibular glands) was noted after the second injection, and the enlarged flagellum of the clitoris was occasionally protruding from the cloacal opening. After four injections the flagellum and the terminal portion of the enlarged clitoris were exhibited almost invariably (Figure I). With further injections the clitoris increased still more in length and diameter until a maximum diameter of about one centimetre at the caudal end and a length of three to four centimetres were attained. At this stage horny spicules were observed on the shaft of the clitoris, similar to those seen on the penis of mature males. The urethral groove on the dorsal surface developed in accordance with the increased size of the organ and reached the depth of three millimetres. Since this enlarged clitoris completely filled the cloacal opening, the urethral groove apparently played an important role, inasmuch as it facilitated or even made possible urination.

(*b*) *Immature Females.*—The larger of the two immature females (body weight, 1·3 kilograms) which received 100 milligrammes of this hormone over a period of two weeks, showed a greatly enlarged and protruding clitoris and an increase in size of the cloacal hillock after this short period of treatment. The clitoris gradually diminished in size; but at the end of six months it was still larger than normal, though it no longer extruded. The younger animal of this series (body weight, 0·8 kilogram) received 10 milligrammes of testosterone propionate per week over a period of seven months. Two weeks after the injections were begun the clitoris and its flagellum were found to be enlarged and appeared externally on micturition. After a further fortnight's treatment the organ was constantly protruded either in a semi-flaccid or in an erect state. Its length was about three centimetres and its maximum diameter (caudal end) 0·9 centimetre, and the shaft was covered with spicules. As the experiment progressed further the clitoris increased in size only slightly, and at the end of five months it was retracted within the cloaca most of the time. Both animals of this group acquired a typically male appearance and behaviour after a number of injections of testosterone propionate.

### Administration of Testosterone Propionate to Males.

The males used in this study were (*d*) one pouch young aged about four months, (*e*) one immature male aged about ten months, and (*f*) one fully grown sexually mature specimen.

### *Changes in and around the Scrotum.*

The scrotum of *Trichosurus vulpecula*, like that of other marsupials, is pre-penile in position, corresponding in situation to the posterior end of the pouch in the female. As already pointed out by Van den Broek,[6] the testicles enter the scrotum at an early age. In a pouch young of about one month of age the testicles appear to have taken up their permanent position in the scrotum. However, about five or six months after birth, when the young has left the pouch, the neck of the scrotum is frequently found to be comparatively broader than at an earlier age, and owing to this broad base some animals of this age or a few months older are capable of retracting one or both testicles half-way out of the scrotum into the inguinal area. During this period of adolescence, in all animals observed so far, the scrotum was a sessile heart-shaped structure which was always somewhat broader than it was long. Further, it may be pointed out that the lower third of the scrotum is covered by a sparse growth of hair. In the same location one may occasionally observe

small amounts of a brownish substance, which seems to stain the scrotal hairs an orange-brown colour, and which suggests the secretion of a pigment similar to that seen in the pouch of females.

When maturity is approached, the neck of the scrotum begins to become elongated and definitely narrower, and the withdrawal of the testes from the scrotum becomes a physical impossibility. If the animal exerts a pull by means of the cremaster muscle the whole scrotum is pulled up towards the abdomen. In the following few months, when the animal is about one year old, the neck lengthens further and forms a band, in the lateral margins of which are the spermatic cords. In the adult sexually mature animal the neck of the scrotum may be several centimetres in length and 0·75 to 1·5 centimetres in width.

(*d*) *Pouch Young.*—The pouch young was aged about three and a half months and was still in the hairless state (body weight, approximately 50 grammes). Before injections were begun the scrotum was a globular sessile structure with practically no visible neck (Figure II);

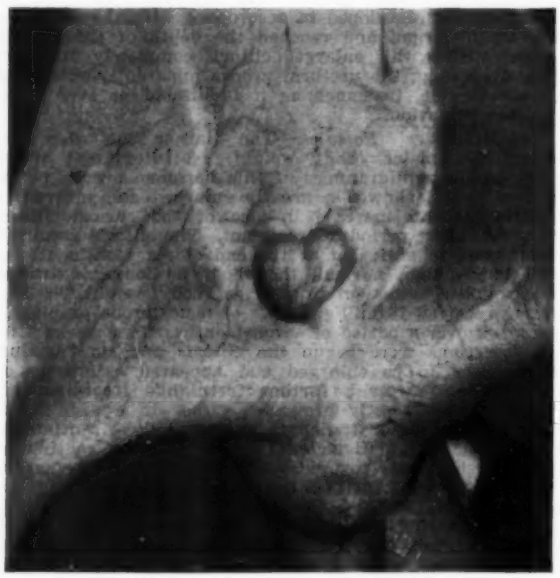

FIGURE II.
Normal appearance of scrotum and cloacal hillock in pouch young aged about three months.

it measured about 0·6 centimetre in diameter and 0·5 centimetre in length. After two weekly injections of five milligrammes of testosterone propionate the scrotal sac became elongated and lax. Its tip presented a redundant and wrinkled appearance. With further similar injections the scrotum became still more elongated (Figure III), reaching a length of 3·3 centimetres and a width of 1·6 centimetres, while in controls of the same age the scrotal sac retained the normal broad heart-shaped structure. This elongated appearance of the scrotum of the injected animal was maintained for the duration of the experiment—that is, for seven months. But in the latter half there was a decrease in size relative to the increase in body weight, and for the last two months of the experiment the scrotum did not increase at all in size, while the animal kept on growing. Around the fourth and fifth months of the experiment fine yellow flakes of pigment were observed over a tip of the scrotum which was covered with more and longer hairs than usual. Furthermore, two folds appeared on either side of the scrotum, roughly overlying the epipubic bones. These gave an impression as though the lips of a large, open, shallow pouch had formed. These folds, however, were not permanent. If they were not present in the resting animal they could be brought out by handling it, and particularly by stroking the mid-line of the abdomen. Moreover, during the last two months of the experiment the scrotal neck had become widened, which enabled the animal to retract the testes. Testes and epididymes showed some abnormal growth after the scrotal sac had already become elongated—that is, about four weeks after the beginning of the injections. About this time the

FIGURE III.
Group (*d*). Elongated pendulous scrotum of possum aged about six months, which had had six weekly injections of five milligrammes of testosterone propionate.

*globi minores* began to increase in length to a considerable degree. After the termination of the experiment the animal was killed. At autopsy each of the *globi minores* measured 1·0 centimetre in length, while the testis and *globus major* together measured also not more than 1·0 centimetre in length (Figure IV). The prostate measured

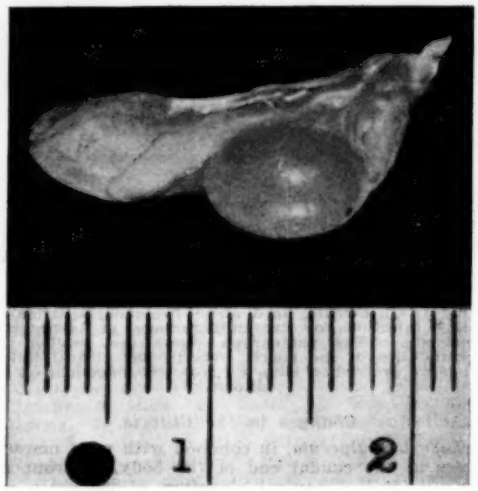


FIGURE IV.
Group (*d*). Showing increased *globus minor* after treatment with testosterone propionate.

2·0 centimetres in length and 1·9 centimetres in width and 1·3 centimetres in depth; it weighed 2·3 grammes, which is somewhat heavier than the weight of the prostate of untreated controls of similar age. Microscopic examination revealed increased fibrosis in the organ.

(*e*) *Immature Male.*—The immature male was aged about ten months (body weight, 1·1 kilograms). Before injections were begun the scrotum was a heart-shaped structure attached to the abdomen by a very short neck, about 0·1 centimetre in length. The scrotum itself measured 2·5 centimetres in width and 2·0 centimetres in length. The penis was not protruding at any time before the experiment was started. After two weekly injections of 35 milligrammes each the scrotum was slightly longer (2·8 centimetres) than it was wide (2·3 centimetres). After further similar weekly injections the scrotum became elongated still more, but did not increase in width. After four weekly injections it measured about 4·0 centimetres in length and 2·5 centimetres in width. Two months after the injections were begun an elongated sheet-like neck, 3·0 centimetres in length, had developed (Figure V). This structure, besides its greater length, was similar in appearance to that seen in older, sexually mature, animals. The testicles appeared to be of approximately normal size and were placed in the distal end of the scrotum. The *globi minores* of the epididymes, however, were enlarged. Two folds simulating a rudimentary pouch also appeared on the lower portion of the abdomen, as were found in the previous animal. After the injections had been maintained for four months the animal was killed. At autopsy a greatly enlarged prostate was noted, weighing 19·5 grammes, or one sixty-third of the body weight (body weight, 1·23 kilograms).

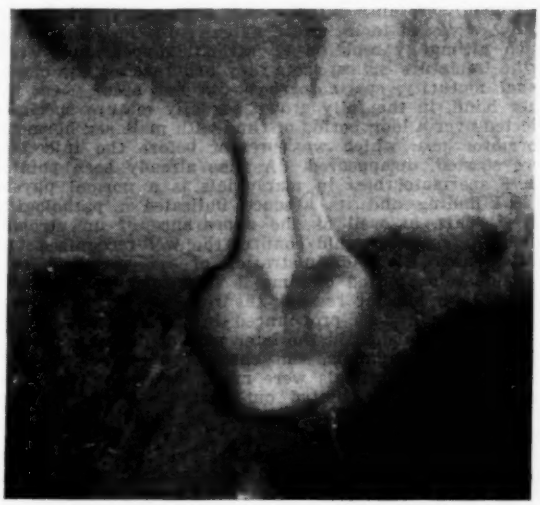

Figure V.

Group (*e*). Elongated scrotal neck in sexually immature possum. The penile flagellum is seen protruding from the cloacal opening.

(*f*) *Sexually Mature Male.*—A large sexually mature male (body weight, 2·1 kilograms) was injected weekly with five milligrammes of testosterone over a period of four months. During this time the scrotum, which was of the usual pendulous shape as that seen in sexually mature males, showed no definite changes; but the spermatorrhœa which was present before the experiment was started disappeared after about two months' treatment.

### *Changes in the Penis.*

The male as well as the female of *Trichosurus vulpecula* possesses at the caudal end of the body a so-called cloacal hillock which contains the bulbo-urethral glands, the *corpora cavernosa* and the penis, and which carries on its apex the external opening of the cloaca; it is in the same location as that of the female and is of about similar size. In the male the cloaca consists of the rectal canal, into which merges the uro-genital canal. The penis always remains hidden in a penis pocket within the cloaca, except during copulation or for short periods during the breeding season, when in sexually mature specimens the erect organ is seen protruding from the cloaca for a distance of one to four centimetres. The organ then measures 0·5 to 1·5 centimetres in diameter, and on its shaft it is covered with small horny spicules. The distal end has an almost flat surface, which is circular. Towards the periphery is attached an elongated structure one centimetre in length—the flagellum. Near the flagellum the urethra opens.

The same males which have already been discussed from the aspect of changes in the scrotum will be described now with regard to changes in the penis.

(*d*) *Pouch Young.*—After the second weekly injection of five milligrammes of testosterone propionate the cloacal hillock increased about threefold in size, forming a cone of about 2·5 centimetres in length and width (Figure VI).

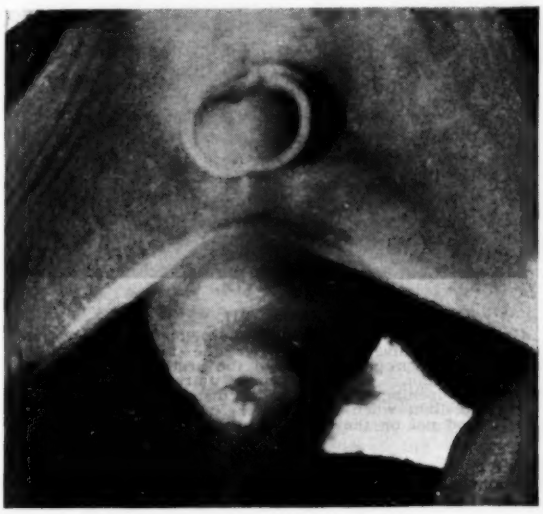

Figure VI.

Group (*d*). Enlarged cloacal hillock after two weekly injections of five milligrammes of testosterone propionate. Note also the wrinkled appearance of the scrotum. Compare with normal appearance as shown in Figure II.

The penis was not yet visible, but could be pushed out from the cloacal opening; it was about 1·5 centimetres in length and 0·2 centimetre in diameter. After two more injections the penis was permanently erected and protruded from the cloacal opening. The cloacal hillock also underwent a further increase in size, which seemed to be due to enlarged bulbo-urethral glands, *corpora cavernosa* and penis. In the next few weeks all of these structures further increased in size, and particularly the penis, which reached a length of 3·0 centimetres and the diameter of about 0·7 centimetre at a time when the body weight of the animal was 350 grammes. After about two months' treatment the penis was found to be protruding only occasionally, and the cloacal hillock also became somewhat smaller. This state remained about the same for the rest of the experiment.

(*e*) *Immature Male.*—As is generally observed with this type of animal, the penis was not visible before injections were started; but within ten days after the injections were commenced (the rate was 35 milligrammes per week) this organ was found to be protruding for a distance of 1·0 centimetre, and an increase in the size of the cloacal hillock was noted. The diameter of the penis was approximately 0·4 centimetre. This represented a very pronounced increase over a short period of time, which must have been due mainly to a permanent state of erection. In controls of similar age the penis hidden in the penis pocket was found to be only about 0·2 centimetre in thickness and 0·6 centimetre in length. With further weekly injections the penis increased up to 3·5

centimetres in length and 0·9 centimetre in diameter; but after a total of four injections it protruded only occasionally, and about two months after the experiment was begun the organ, although still large, was hardly ever seen protruding.

(*f*) *Sexually Mature Male.*—Generally speaking, no such distinct influence of testosterone propionate could be noted in the sexually mature male as in younger animals, with the exception that during breeding season the penis was seen to be protruding more frequently than in controls. The cloacal hillock, however, seemed to be somewhat larger and firmer than in controls.

Figure VII.

Group (*d*). Precocious penile development in possum aged about five months after the administration of testosterone propionate. Note the urethral opening and the flagellum. In fully grown untreated animals the urethral opening is found on the distal end right beneath the flagellum when the penis is in a state of erection, and not on the shaft as shown in the picture.

## Discussion.

Recently in the United States of America Burns[6,7] and Moore[8] have carried out experiments similar to those described in this paper on the Virginia opossum (*Didelphys virginiana*). However, the animals of the American workers were considerably younger when the injections with testosterone propionate were commenced. They were either newly born pouch young or pouch young not more than a few days old. In any case these animals had not reached the stage of sex differentiation when injections were started. In discussing his experimental findings, Burns stressed the fact that no changes were found in either the pouch or the scrotum following the injection of this hormone. Moore in his series does not report any changes in these organs.

But in the immature *Trichosurus vulpecula* aged about three months or more, definite changes occurred in the pouch and scrotum. In the pouch the initial response was an increase in size of the mammæ, which in some instances was accompanied by secretion from the nipples. Then thickening and puckering of the lips of the pouch were observed and pigment became visible as described. These changes were similar in character to those seen after the administration of moderate doses of œstrogen.[1]

With regard to the changes observed in the scrotum, it appeared that in immature possums this organ had a specific response to testosterone propionate. In the younger animal (aged three to four months) it rapidly proliferated to form an elongated, rather narrow and pendulous sac. This was accompanied by an elongation of the epididymes, most pronounced in the region of the *globus minor*, which became about the same size as the testis and *globus major* together. In the older animal (aged ten months) the broad sessile scrotum containing two well-developed testes had already formed before injections were started. Consequently the changes were not so marked as those observed in the younger animal; but they still were typical, inasmuch as long before sexual maturity was reached an elongated scrotal neck had formed. Also a definite hypertrophy of the *globi minores* was noted. This elongation of the scrotum may be interpreted as a precocious development heralding the premature development of the scrotal neck, which in normal circumstances would appear much later in life. The elongation of the scrotum seemed to precede a corresponding elongation of the spermatic cord, as evidenced by the younger animal of our series. It apparently also preceded the pronounced enlargement of the lower poles of the epididymes, indicating an independent physiological response of the scrotum as has been pointed out before, and a precocious or exaggerated testicular descent seemed to be secondary to alterations in the scrotum.

The scrotal sac, besides becoming altered in shape after injections of testosterone propionate, also showed an increased growth of hair around its lower third. Moreover, during certain phases of the experiment pigment was found to be secreted around the tip of the scrotum, and it was present to a larger degree than in untreated controls at any time. This observation reminded us of a similar secretion of pigment in the pouches of females, as has been described in an earlier part of this paper and as has been noted after the injection of œstrogens.[1] In this connexion the appearance of folds giving the impression of the formation of a pseudopouch may be mentioned, and reference may be made to similar observations after the injection of œstrogens into males.[9]

After the administration of testosterone propionate over several months it was noted that the excessive development of pouch, scrotum, clitoris and penis diminished and finally regressed to a certain extent. In the females the pouch ultimately took on an atrophic appearance, while in the immature males, after they had reached the age of sexual maturity, spermatorrhœa did not occur. On the other hand, in the fully grown sexually mature specimen injected over a long period of time with male sex hormone, spermatorrhœa, which was present before the injections were started, disappeared. As has already been pointed out,[10] spermatorrhœa in marsupials is a normal physiological finding and its absence indicates a pathological state. This, as well as the appearance of an atrophic pouch in females, would confirm the well-recognized fact that the excessive administration of sex hormones over a considerable period of time is harmful to the gonads. Probably for similar reasons the response of clitoris and penis, although very pronounced in the first few weeks, distinctly diminished in the later part of our experiments. As in other mammals, the changes observed in older sexually mature animals were much less conspicuous. It must, however, be pointed out that these were treated over a comparatively short period, or with a rather small dosage.

The experiments on the immature *Trichosurus vulpecula* illustrate well the recently recognized ambisexual properties of testosterone.[11] The androgenic effects are exhibited by the secondary male sex structures and their female homologues. In the female they are manifested by hypertrophy and protrusion of the clitoris and an increase in the size of the cloacal hillock. In the male, elongation of the scrotum and hypertrophy of the penis and cloacal hillock were observed.

Gynæcogenic effects have been observed on female secondary sex structures; they were manifested by changes in the pouch, including pigment formation and mammary hypertrophy. In the male such changes as temporary widening of the scrotal neck, the formation of a pseudopouch and the appearance of pigment on the scrotum may be regarded as evidence of gynæcogenic action.

On this occasion it must also be pointed out that, contrary to some recent statements regarding the diminution in size of the prostate in general caused by the administration of testosterone propionate in the marsupial *Trichosurus vulpecula*, this was not observed, and in young animals an increase in size was noted and in a sexually mature animal increased fibrosis. This is also of interest in view of the fact that large doses of œstrogens were found to decrease the size of the prostate of this animal.[12]

The observations recorded in this paper in conjunction with previously reported findings[1,2,3,4,5,9,10,11] indicate the

usefulness of our common Australian possum for studies of this nature. They further demonstrate the wealth of information to be gained from such investigations.


### Summary.

If testosterone propionate is administered to sexually immature possums (*Trichosurus vulpecula*) of both sexes, pouch, scrotum, clitoris and penis show a pronounced response. The lips of the pouch become thickened and puckered, the scrotum is elongated to a considerable degree, while the clitoris and penis both undergo hypertrophy.



### Acknowledgement.

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## THE RELATIVE ERROR IN EXAMINING SWABS FOR CORYNEBACTERIUM DIPHTHERIÆ BY THE LÖFFLER SLOPE AND BY THE CLAUBERG PLATE.[1]


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RECENT work has shown that the time-honoured method of examining a stained smear of the growth on a Löffler slope may fail to reveal *Corynebacterium diphtheriæ* originally present on swabs; this work has been carried out by Clauberg (1931), Himmelweit (1932), O'Meara and Parish (1933), Schmitt (1933), Frobisher and van Volkenburgh (1935), Gundel and Liebetruth (1935), Hasenbach (1935), Bender and Bruns (1936), Parish (1936), Kerrin and Gaze (1937), Neill (1937), Wilson and Goldsworthy (1938), Shone *et alii* (1939). A new method, that of inspecting with the naked eye the colonies on the surface of various tellurite media, has been shown to reveal *Corynebacterium diphtheriæ* in from 3% (Gundel and Liebetruth, 1935) to 60% (Schmitt, 1933) more swabs than the Löffler slope method.

The use of tellurite blood agar plates has made it relatively easy to isolate *Corynebacterium diphtheriæ* and so to prove the methods used in examining swabs for this organism.

In the present work an attempt has been made to determine not so much the relative proportion of swabs reported as "positive" by the two methods, which has already been done by others, but rather the proportion erroneously reported as "positive".

### Materials and Methods.

One thousand one hundred and fifteen swabs were examined; 549 were from patients recently admitted to hospital suffering from diphtheria; the results of examination of the first 396 of these swabs have been published previously (Wilson and Goldsworthy, 1938); most of these were throat swabs. The remaining 566 were from in-patients waiting to be "cleared" before their discharge from hospital, or from out-patients suspected of diphtheria or from suspected carriers; about equal numbers of these swabs were from the nose and throat respectively.

Each swab was rubbed first over a Löffler slope, then over a Clauberg (1931) plate ("Clauberg II"). After incubation overnight, a Neisser-stained smear of the growth on the Löffler slope was examined; in addition, 233 of the Löffler cultures were reexamined next day. The Clauberg plates were examined with the naked eye and with the colony microscope (×15) after incubation overnight; in addition, those not showing colonies of *Corynebacterium diphtheriæ* were reexamined next day. Nearly all cultures were examined by two observers. When the results of examining the corresponding Löffler and Clauberg cultures disagreed, the growth on the Löffler slope was suspended in broth and plated out on Clauberg's medium.

Colonies suspected of being *Corynebacterium diphtheriæ* were isolated in pure culture and their fermentation reactions were then examined in glucose, saccharose and glycogen. In order to detect strains of the *intermedius* type, colonies of those strains of *Corynebacterium diphtheriæ* which did not ferment glycogen were examined on blood agar plates (Wilson and Goldsworthy, 1939), as also were colonies of most of the strains which fermented glycogen.

In order to observe whether the growth of some strains of *Corynebacterium diphtheriæ* was suppressed on Clauberg's medium, five *gravis* and five *mitis* strains were grown in pure culture on this medium, containing either the usual amount (0·04%) of potassium tellurite or half this amount, and on 10% sheep blood agar. In Table I are shown the number of colonies which grew after the plates had been sown each with 0·1 cubic centimetre of the same pure suspension of each strain.

TABLE I.

*The number of colonies of five* mitis *and five* gravis *strains of* Corynebacterium diphtheriæ *growing on plates of* (i) *blood-agar and* (ii) *Clauberg's medium, containing 0·04% or 0·02% potassium tellurite, sown with the same number of organisms of each strain.*

| | Blood Agar. | Clauberg. | |
|---|---|---|---|
| | | 0·04% | 0·02% |
| *Mitis:* | | | |
| Atkins .. .. .. | 44 | 45 | 48 |
| Ath. .. .. .. | 57 | 24 | 57 |
| B. .. .. .. | 51 | 50 | 60 |
| F. .. .. .. | 16 | 6 | 19 |
| S. .. .. .. | 49 | 19 | 46 |
| *Gravis:* | | | |
| McE. .. .. .. | 36 | 28 | 47 |
| Black .. .. .. | 30 | 27 | 24 |
| K. .. .. .. | 27 | 16 | 21 |
| L. .. .. .. | 23 | 8 | 15 |
| Mx. .. .. .. | 29 | 19 | 33 |

### Results.

*Corynebacterium diphtheriæ* was isolated from 453 swabs; 332 strains were *gravis* in type, 17 were *intermedius*, 104 were *mitis*.

[1] This work was carried out with the aid of grants from the Commonwealth Government and from the National Health and Medical Research Council.

From Table II it is seen that the results of using the Löffler and Clauberg methods agreed for 975 swabs (395 swabs Clauberg "+", Löffler "+"; 580 swabs Clauberg "–", Löffler "–"), but disagreed for 140 swabs (86 Clauberg "+", Löffler "–"; 54 Clauberg "–", Löffler "+")—that is, the methods disagreed for 12·5% of the 1,115 swabs examined.

The relative error of the two methods is shown in the lower line of Table II. *Corynebacterium diphtheriæ* was not isolated from 19% of the swabs reported as Clauberg "+", Löffler "–", or from 85% of the swabs reported as Clauberg "–", Löffler "+".

With the Clauberg method colonies of diphtheroids or of cocci were mistaken occasionally for colonies of *Corynebacterium diphtheriæ*. With the Löffler method, diphtheroids, morphologically resembling *Corynebacterium diphtheriæ* were mistaken for them, more especially after forty-eight hours' incubation. It was found also, when the Löffler cultures were plated out, that *Corynebacterium diphtheriæ* was apt to be missed in stained smears of the Löffler cultures, especially when the numbers were small, as judged by the fact that only a few colonies of *Corynebacterium diphtheriæ* were present on the corresponding Clauberg plate.

TABLE II.[1]

*Comparison of results of examination of 1,115 swabs for* Corynebacterium diphtheriæ *on Clauberg plates (macroscopic diagnosis) and on Löffler slopes (microscopic diagnosis). The numbers in brackets are percentages of the numbers reported as "positive".*

| | Clauberg "+". Löffler "+". | Clauberg "+". Löffler "–". | Clauberg "–". Löffler "+". |
|---|---|---|---|
| Reported as "positive" .. | 395 | 86 | 54 |
| Disproved .. .. .. | 20 (5·1) | 16 (18·6) | 46 (85·2) |

[1] 580 swabs were Clauberg "–", Löffler "–".

## Discussion.

Unfortunately most previous reports appear to have been based on bacterial and colonial morphology only; the identity of the organisms believed to be *Corynebacterium diphtheriæ* was not proved, and therefore the proportion of swabs erroneously reported as "positive" by each method was not ascertained. In the three reports mentioned below it is clearly stated that the organisms were isolated and their identity was proved by fermentation or virulence tests.

O'Meara and Parish (1933) subcultured on Horgan and Marshall's (1932) tellurite plates 258 Löffler slope cultures which had been reported as "negative", and isolated from them 22 strains of *Corynebacterium diphtheriæ*, of which nine were virulent.

Frobisher and van Volkenburgh (1935) isolated many virulent and avirulent strains in similar circumstances.

Kerrin and Gaze (1937) examined 16,000 swabs on Löffler slopes and on tellurite slopes; the growth on the latter was inspected with a hand lens; 1,514 were "positive" on both media, 440 on the tellurite medium alone, 7 on Löffler's medium alone. Of the 440 strains isolated from swabs which were "positive" on the tellurite medium alone, 387 were virulent.

In the present work a discrepancy was found between the reports by the two methods; but, while mistakes were made with both methods, they were more numerous with the Löffler method. It can be calculated from Table II that 136 errors were made by the Löffler method and 44 errors by the Clauberg method. An analysis, based on Table II, of the mistakes that were made in each of the methods reveals the following points.

*The Clauberg Method.*—Errors of commission were 36 (7·5%) out of 481 swabs reported as "positive". With Clauberg plates even an experienced observer is apt to err occasionally in his interpretation of the colony form. However, the identity of the organisms of a suspected colony can be readily established by subculture from the suspected colony into glucose and saccharose medium, tubes of which should be kept ready for the purpose. Errors of omission were very few, since of 54 cultures which were reported Löffler "+", Clauberg "–", *Corynebacterium diphtheriæ* was isolated in only eight instances. *Corynebacterium diphtheriæ* was isolated from 453 swabs, so that these eight errors of omission represent only 1·8% of the swabs that were proved to be "positive".

*The Löffler Method.*—Errors of commission were 66 (14·7%) out of 449 swabs reported as "positive". It must be assumed that in these swabs diphtheroids were mistaken for *Corynebacterium diphtheriæ*. This error is more apt to occur after forty-eight hours' incubation on the Löffler medium. It is possible that *Corynebacterium diphtheriæ* was present in some of these swabs, but that when the growth on the Löffler medium was plated out on the Clauberg medium, colonies of *Corynebacterium diphtheriæ* were not recognized or that the growth of *Corynebacterium diphtheriæ* was suppressed. It seems unlikely that the colonies of *Corynebacterium diphtheriæ* were missed when replating on Clauberg's medium was carried out, because errors with this medium were errors of commission rather than of omission. Although it is possible that the growth of *Corynebacterium diphtheriæ* was suppressed when replating on Clauberg's medium was carried out, this also seems unlikely, since the results given in Table I show that potassium tellurite in a concentration of 0·04% inhibits the growth of *Corynebacterium diphtheriæ* but slightly. Errors of omission were numerous, since of 86 swabs reported as Clauberg "+", Löffler "–", *Corynebacterium diphtheriæ* was isolated in 70 instances. Since *Corynebacterium diphtheriæ* was isolated from 453 swabs, these 70 errors of omission represent 15·4% of the swabs that were proved to be "positive". Errors of omission may arise from the use of Löffler's medium in two ways. First, some *gravis* strains, especially when grown on poorly made Löffler's medium, may be difficult to recognize in stained smears because coccoid or other aberrant forms may be assumed, and metachromatic granules may be few and small or apparently absent. There is reason to believe, however, that the Löffler's medium used in the present work was at least as good as that generally used in other laboratories; moreover, it was checked repeatedly with *gravis* strains. Secondly, if only few *Corynebacterium diphtheriæ* are present on a swab, they may be more apt to be missed by the microscopic (Löffler slope) method than by the macroscopic (Clauberg plate) method.

*Comparison of Methods.*—To sum up this analysis, the error of commission with the Clauberg method was 7·5%, with the Löffler method 14·7%; the error of omission with the Clauberg method was 1·8%, with the Löffler method 15·4%.

## Summary.

1. One thousand one hundred and fifteen swabs were examined for *Corynebacterium diphtheriæ* by the Löffler slope method (microscopic) and by the Clauberg plate method (macroscopic). Whenever a swab was reported as "positive" by either method, an attempt was made to isolate and identify the organism. *Corynebacterium diphtheriæ* was identified in 453 out of the 1,115 swabs.

2. There was a considerable discrepancy between the results obtained by the two methods, and while mistakes were made by both methods, they were more numerous with the Löffler method—namely, 136 errors with the Löffler method, 44 errors with the Clauberg method.

3. An analysis of the errors showed: (*a*) that the error of commission (reporting of a swab as "positive" when *Corynebacterium diphtheriæ* was not present) with the Löffler method was 14·7%, with the Clauberg method 7·5%; (*b*) that the error of omission (reporting of a swab as "negative" when *Corynebacterium diphtheriæ* was present) with the Löffler method was 15·4%, with the Clauberg method 1·8%.

4. Reasons for these errors are discussed. Even after experience has been gained in the interpretation of the colony form on Clauberg's medium, doubt may arise occasionally; it is then easy to prove the identity of the organism of a suspected colony by its fermentation reactions, whereas the identity of suspected *Corynebacterium diphtheriæ* seen in the stained smear of a Löffler culture can be proved less readily.

## Acknowledgement.

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### Addendum.

Since this paper was submitted for publication two further comparisons of the results of using Löffler's and various tellurite media have been reported (M. Welsch, G. Demelenne-Jaminon and J. Thibaut, *Comptes rendus des séances de la Société de biologie*, Volume CXXXII, Number 24, 1939, page 326; and K. E. Cooper, F. C. Happold, K. I. Johnstone, J. W. McLeod, H. E. de C. Woodcock and K. S. Zinnemann, *The Lancet*, Volume CCXXXVIII, May 11, 1940, page 865). Each report stated that *Corynebacterium diphtheriæ* was recognized more readily by means of the tellurite media than by means of Löffler's medium. The results reported in the present paper support the opinion expressed by Cooper and his associates that "those bacteriologists who continue to depend entirely on this [Löffler's] medium are doing second-rate bacteriological work so far as diphtheria is concerned".

## Reports of Cases.

### HYDRANENCEPHALY.


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HYDRANENCEPHALY is not, as the name introduced by Cruveilhier in his famous *"Traité de l'anatomie pathologique générale"* over 100 years ago might suggest, a combination of a hydrocephalus and an anencephaly, but a condition in which some features of each are present and others absent. It is extremely rare. Only a very few cases have been described and none exactly resembles the others; there are often considerable variations. A report of such a case seems therefore to be well justified.

### Clinical Record.

A woman, aged twenty-one years, who had no history of a previous illness, was delivered of her first child, a female, 50 centimetres in length and weighing 2,780 grammes. It was a normal vertex presentation; the delivery was easy, without abnormal features; the placenta was circumvallate, but was otherwise of normal structure. The baby was quite well developed and showed no malformations; its head was well formed, although it was noticed that the sutures were rather wide and the fontanelles large. It took the breast like any other normal child. Only one unusual symptom was noticed: the head felt always slightly cooler than that of other babies. For five days it developed in the normal way. During the next two days subnormal temperatures were found, and death occurred on the seventh day without any definite clinical symptoms or signs.

### Post-Mortem Findings.

At autopsy the normal configuration of the head was conspicuous. The sutures were wider than usual, but nowhere to such an extent as is often seen in cases of hydrocephalus. When the skull was opened a large amount of straw-coloured fluid escaped. A closer inspection showed that the dura was apparently firmly attached to the inner surface of the skull bones. No traces of the cerebral hemispheres were observed. A kind of membrane obscured the view of the base of the skull in the anterior and medial fossæ, while the tentorium covered the posterior fossa and from it the falx arose in the normal way.

At this stage of the autopsy it was decided to fix the whole head in order to gain a better idea of the structures beneath these membranes by a later bisection. The result is shown in Figures II and III. The cerebral hemispheres and the *corpus callosum* are completely absent; some mid-brain tissue is present beneath the membrane described above, but it is impossible to recognize normal structures. The pons, cerebellum and *medulla oblongata* are apparently well formed.

FIGURE I.

The examination of the thoracic and abdominal cavities revealed no malformations or pathological conditions.

A detailed histological examination of the parts of the brain which were partly or completely developed has not been made. It could have been done only by the destruction of the macroscopic specimen, and this seemed unnecessary. Such examinations have been made in two of the known cases, and they resulted only in findings which were to be expected in the absence of cerebral hemispheres; but they did not contribute to the explanation of this rare condition.

An examination, however, of the membrane which separated the large cavity from the rest of the mid-brain, and of the lining of the cavity at the inner surface of the skull bones, seemed to be important. It was seen that at this site there was only the tissue of the *dura mater*; no nervous elements were present. The membrane, however, above the mid-brain was composed to a large extent of immature nervous elements.

### Discussion.

Before an attempt is made to explain this strange condition, it is necessary to review in some detail the few cases already known. There are two or three reports in the French literature, but these were published over thirty years ago and the journals are not available in Australia. No report in English literature has come to my knowledge. There remain, therefore, only three reports in the German literature for comparison with the present case. The latest publication is that by Hurowitz[1] (1936). His case is rather different. The head of the baby was considerably

FIGURE II.

increased in size (perforation had to be performed in order to make delivery possible). The forehead was not properly developed, so that the appearance of the baby was more consistent with anencephalus. Cerebral hemispheres were missing, but some folded membranes floating in the fluid were found in their place. The structure of these membranes was rather similar to that of the membrane described above. Mid-brain, pons, cerebellum and *medulla oblongata* were normal.

The report by Spielmeyer[2] (1905) is of great interest, as this extremely rare condition occurred in non-identical twins. Both had normally formed skulls. The first had no cerebral hemispheres whatsoever; the anterior and middle cranial cavities were empty, and the posterior cavity was covered by the tentorium. Attached to the *sella turcica* was a cyst about the size of a walnut. The mid-brain was only partly present; pons, cerebellum and medulla were normal. In the second twin's skull cavity there was a large sac containing 280 cubic centimetres of fluid, which was attached only to the base and not to the walls of the skull. Its basal parts contained some brain rudiments (possibly thalamus or hippocampus). The structures from the *corpora quadrigemina* downwards were normal. The walls of the cystic formations consisted of meningeal and immature nervous tissue.

The third paper by Edinger and Fischer[3] (1913) contains a description of the most extraordinary case of this group. Here the substance of the cerebral hemispheres had almost completely disappeared, but the pia was still present, and it appeared as though someone had made a model of the cerebral hemispheres from a very thin and translucent material. The cerebral hemispheres were not replaced by two large sacs only, but every part of them was represented by individual cysts, so that the two large sacs were subdivided into numerous smaller cysts. Even a cystic representation of the *corpus callosum* was found. The mid-brain was only partly developed, while the lower parts were normal.

This short summary shows that no case resembles the others very closely. They have all in common that the substance of the cerebral hemispheres is missing, that the mid-brain is only partly present, and that the lower structures are normal. They all differ in whatever structures are found replacing the cerebral hemispheres. The cases tend to arrange themselves into a certain order, from the pia model in Edinger and Fischer's case, through the cystic and membranous formations in Spielmeyer's and Hurowitz's cases to the complete emptiness of the cavity in my case. The unusual features of Hurowitz's case which make it less comparable with the others have been mentioned above.

### Comment.

It is very difficult to form an opinion about the ætiology and subsequent development of this condition. The presence of these membranous and cystic rests of the cerebral hemisphere makes it clear that the condition cannot be due to a primary non-formation of the cerebral hemispheres. The fact that the skull was normally developed in all but one case seems to indicate that the onset of this condition has to be placed in a rather late period of the pregnancy. Even the case presented here does not contradict that assumption. The absence of any cystic rests of the cerebral hemisphere may suggest a primary malformation; but the fact that the basal membrane above the mid-brain contained immature nervous tissue suggests that the hemispheres had been replaced by one large sac which completely filled the cavity of the skull. Its original structure is now to be seen only in the basal part. Its other portions have become attached to the walls of the skull, and their original structure has disappeared by atrophy so that now only the dura is left.

If the condition is not a primary malformation, what then can it be? Two suggestions have been made: it has been considered to represent either a most advanced stage of hydrocephalus or an extreme degree of porencephaly. Against hydrocephalus is the normal development of the skull in nearly all cases; there are usually no signs of increased intracranial pressure, and all the rests of the cerebral hemispheres found cannot be very well explained in that way. Edinger and Fisher's case clearly contradicts such an explanation. With regard to porencephaly, there are no findings which would be incompatible with such a conception. The difficulty in accepting such an explanation is more a matter of quantity than one of quality. The most extensive cystic formations in cases usually considered to be of porencephaly never reach anything like those found in the cases described above.

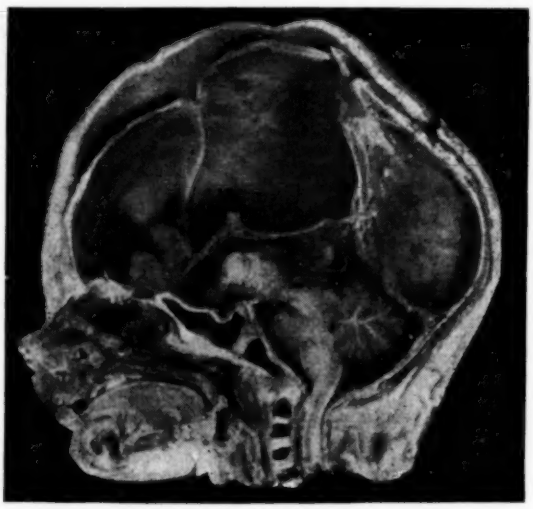

FIGURE III.

Nevertheless, porencephaly is likely to be the most closely related condition. The placing of the condition in this category does not offer a solution of the problems concerned. The causes of porencephaly are likewise rather obscure. There is reason to assume that in such cases destruction of the brain substance is due to vascular processes, and Spielmeyer has found such changes in his two cases. The question arises as to what are the causes for these vascular changes, and here the opinions are divided between those who suggest a primary malformation of the vascular system and those who are inclined to hold inflammatory or traumatic processes responsible. Support for both suggestions has been brought forward, but a final decision has not yet been reached.

Finally let me add a few words about the clinical behaviour of these children. In Hurowitz's case the head of the fœtus had to be perforated to make delivery possible. The twins of Spielmeyer and the baby reported in this paper lived for about one week. The twins died from bronchopneumonia.

In my case no definite lesions in other organs than the central nervous system were found. All these three children behaved absolutely in the same way as other babies during the first week of their life.

The most remarkable case, however, not only from the pathological, but also from the clinical point of view, is Edinger and Fischer's case. This child lived for three and three-quarter years. It took the breast for six weeks and had then to be fed at first by a spoon and later on from a bottle. It never gave any indication that it was hungry. It slept continuously during the whole of the first year and had to be awakened to be fed. There were no voluntary movements. There was hardly any functioning of the organs of sense. It sucked the bottle only when it contained milk, but it never swallowed any other food. It closed its eyes when exposed to bright light, but never followed with the eyes any object placed in front of it and never recognized the mother. It never reacted to any noise or pinching. During the second year it began to scream with a rather loud voice and did so for many days and nights continuously. Only by rubbing the head was the mother able to quieten it. Feeding became more and more difficult, starvation developed and finally a slight infection terminated this kind of life.

The authors draw some comparisons with animals from which the cerebral hemispheres have been removed for experimental purposes. From the fact that such animals are, after a short time, able to achieve much more than this child ever did, they stress the point that in human beings the cerebral hemispheres are much more important even for the ordinary functions of the body than they are in other mammals. Although this is undoubtedly correct, their conclusion that a child without cerebral hemispheres is less efficient than an animal without them does some injustice to human beings. All such animals had gained control over their organs long before they were operated on. This child had never had a chance to learn anything which could be done under the control of lower centres after a destruction of the higher ones. The comparison therefore is not quite fair.

### Summary.

A case of hydranencephaly is presented. The classification and the causes of this condition are discussed and a few available similar cases are referred to in some detail.

### References.

(1) J. Hurowitz: *"Über einen ungewöhnlichen Fall von Hydromerencephalie", Schweizer Archiv für Neurologie und Psychiatrie*, Volume XXXVIII, 1936, page 207.
(2) L. Edinger and B. Fischer: *"Ein Mensch ohne Grosshirn", Pflüger's Archiv für die gesamte Physiologie*, Volume CLII, 1913, page 535.
(3) W. Spielmeyer: *"Ein hydranencephales Zwillingspaar", Archiv für Psychiatrie und Nervenheilkunde*, Volume XXXIX, 1905, page 807.

## THE SIGNIFICANCE OF THE ASCHHEIM-ZONDEK TEST IN THE EARLY DIAGNOSIS OF CHORIONEPITHELIOMA.

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CHORIONEPITHELIOMA is stated to follow hydatidiform mole in 5% of cases. Diagnosis of the condition is often impossible from the clinical findings alone, and the examination of scrapings may not establish a definite diagnosis. It has been recently suggested that in such cases the Aschheim-Zondek reaction might lead to an accurate diagnosis. A case which illustrates these difficulties is the subject of this paper.

### Clinical Record.

H.G., aged twenty-nine years, was the mother of two children, the younger child being three years old. She was admitted to hospital on October 15, 1939. She had had pneumonia at the age of two years, but had had no other illness.

The menses had been regular up till August 3, 1939, when the last menstrual period was normal. Morning sickness had started over a month before admission. Two weeks later spontaneous vaginal hæmorrhage was noticed, followed in a week by swelling of the abdomen. Early on the morning of her admission to hospital she began to lose blood freely. She had lost about a cupful of blood by the time of her admission, but had had no pain.

Examination revealed a healthy-looking woman with a temperature of 99° F.; her pulse rate was 112 and the respirations numbered 18 per minute. The systolic blood pressure was 120 and the diastolic pressure 70 millimetres of mercury. The apex beat was in the fifth intercostal space inside the nipple line. There was a systolic murmur at all areas. The abdomen moved well with respiration. The lower portion of the abdomen was prominent—the size of a twenty-two weeks' pregnancy. The uterine wall was soft, and no other mass was palpable in the abdomen. A vaginal examination revealed slight bleeding. The os was pointed downwards and admitted the tip of a finger. No vaginal tenderness was present on examination. The fornices were clear. It was not possible to feel the level of the fundus with certainty.

On October 17, 1939, the patient was sent for a dilution Aschheim-Zondek test and an X-ray examination. The radiological report was as follows:

> No fœtal skeleton shown, but it has to be remembered that before mid-term absence of a fœtal skeleton does not exclude pregnancy. Circular calcifications below the right dome of the diaphragm suggest old hydatid cysts.

The pathologist reported on the Aschheim-Zondek test in the following terms:

> Positive in dilutions up to 1 : 249, *i.e.*, at least 250,000 units of gonadotropic hormone present. Hydatidiform mole very likely.

On October 28, 1939, the patient was given medical stimulation, with the addition of one cubic centimetre of pituitrin; there was no result. The uterus now appeared to be enlarged to the size of about a twenty-six weeks' pregnancy. A second Aschheim-Zondek test showed that at least 300,000 units of hormone were present.

On October 30, 1939, at 4.30 p.m., very severe hæmorrhage commenced, and mole tissue was expelled. The uterus was packed. One hour later, under an ether anæsthetic, a large quantity of mole tissue was removed and the uterus was packed with iodine gauze. The patient showed signs of shock at the end of the operation. On October 31, 1939, the packing was removed and no bleeding occurred.

On November 2, 1939, the pathologist reported as follows:

> All the villi are considerably distended. The stroma is œdematous. There is a marked overgrowth of chorionic epithelium, but not more than is usually found in cases of hydatidiform mole.

On November 4, 1939, the patient was allowed out of bed, and on November 5, 1939, she was discharged from hospital.

On November 13, 1939, she was readmitted to hospital on account of a fair amount of yellowish discharge. On the previous night (about nine hours earlier) hæmorrhage began *per vaginam* and some clots were discharged; otherwise she felt well. On examination there was no tenderness or rigidity in the abdomen. The uterus was palpable in the right iliac fossa; it was enlarged to the size of a twelve weeks' pregnancy. Old clots were present in the introitus and the cervix was patulous. There was a mass on the right of the fundus, probably attached to it, but not arising out of the pelvis.

On November 17, 1939, the patient felt well. By December 4, 1939, the uterus was anteverted and mobile, and of normal size. There was no thickening to be felt in the parametrium. The radiologist reported as follows on an X-ray film of the chest:

> Adhesions at the right base associated with the underlying subphrenic hydatid, but otherwise chest normal. No secondaries are obvious.

On December 20, 1939, the patient was discharged from hospital in good health. An Aschheim-Zondek test was performed before discharge; with undiluted urine the result was positive, and with dilutions of 1 : 29 or higher it was negative.

On January 15, 1940, the patient was readmitted to hospital, feeling well. She had not had a menstrual period since her discharge from hospital, but had had a small amount of hæmorrhage at irregular intervals. A vaginal examination was made. The os was patulous, and the uterus was anteverted, mobile and enlarged; its condition was consistent with an eight weeks' pregnancy. The fornices were clear.

On January 17, 1940, an endoscopic examination was made and curettage was performed. The interior of the uterus was smooth and no abnormality was observed. With difficulty a small amount of tissue was obtained for microscopic examination; this gave no indication of chorionepithelioma. On January 20, 1940, the Aschheim-Zondek test with undiluted urine elicited a positive reaction. On January 23, 1940, the Aschheim-Zondek test was again performed. With dilutions of 1 : 9 and 1 : 29 the result was positive in reactions 2 and 3; with a dilution of 1 : 49 it was positive in reaction 2 only; with a dilution of 1 : 149 there was no reaction. On January 30, 1940, the Aschheim-Zondek test was again made. With a dilution of 1 : 49 there was now a positive response in reactions 2 and 3; with a

dilution of 1 : 99 there was a positive response in reaction 2; with dilutions of 1 : 149 and higher there was no reaction.

On January 31, 1940, total hysterectomy was performed. The right Fallopian tube and ovary and the left tube were removed; the left ovary could not be found.

The specimen is shown in Figure I. The uterus is somewhat enlarged and has a fairly wide cavity and a thickened wall. A hæmorrhagic tumour of about the size of a cherry is to be seen. It protrudes only very slightly into the cavity of the uterus, but penetrates more than half the thickness of the wall of the uterus. In the microscopic sections the tumour is seen to be composed of very irregular arrangements of syncytial elements. Groups of Langhans's cells are to be found here and there. No rests of chorionic villi were seen in the sections. The right ovary is considerably enlarged. On section it is seen to be a multilocular cyst filled with greyish gelatinous material. The thin walls of the individual cysts often have a yellowish appearance. The microscopic examination confirmed the naked-eye diagnosis of a lutein cyst.

After a somewhat stormy convalescence, during which paralytic ileus occurred, the patient made a complete recovery. She was discharged from hospital on April 18, 1940. During her convalescence three Aschheim-Zondek tests were performed, one week, six weeks and twelve weeks after operation. The results were all completely negative.

Figure I.

## Summary.

After the removal of a hydatidiform mole the response to the Aschheim-Zondek test did not become completely negative. With undiluted urine it remained positive; but with dilutions as low as 1 : 29 it was negative six weeks afterwards.

Twelve weeks after expulsion of the mole the test revealed a definite rise in the hormone contents of the urine, and this was even more pronounced in the thirteenth week. The patient was at that time in good general health and had no symptoms. The endoscopic investigation revealed a smooth cavity without any growth, and the histological examination of curetted material gave no evidence of a tumour. Total hysterectomy was performed and a chorionepithelioma the size of a cherry was found in the uterine wall.

## Comment.

The Aschheim-Zondek test and its modifications are based on the fact that during pregnancy the placenta secretes a hormone which is closely related to the gonadotropic hormone of the pituitary gland. The amount secreted varies considerably. It reaches its maximum in the earlier months of pregnancy, but very seldom are amounts higher than 30,000 mouse units per litre found.

In the presence of a hydatidiform mole the hormone contents of the urine are usually in proportion to the size of the mole. In the majority of cases excessive amounts of hormone averaging 300,000 mouse units per litre are present. Chorionepithelioma, as examination in numerous cases has shown, occupies an intermediate position. Hormone amounts usually vary around 100,000 mouse units per litre. In chorionepithelioma there is often no proportional relationship between the size of the tumour and the amount of hormone. Small tumours are able to produce large amounts of hormone.

No biological test is correct in 100% of cases, and it is important to know under which condition errors may be encountered when the Aschheim-Zondek test is being applied for the detection of a mole or chorionepithelioma.

The first condition which has to be excluded is a new pregnancy. Secondly, it has been reported that a hydatidiform mole or chorionepithelioma was found in spite of a negative response to the Aschheim-Zondek test. That is very unlikely to occur, and faulty technique might account for it. In a few cases, in which the reports are beyond doubt, it has been shown that in such an instance the growth was separated from the uterine tissue by a fibrinous barrier through which, apparently, the chorionic hormone could not penetrate. Such an occurrence, however, does not diminish the value of a positive response to the test. Excessive amounts of hormone without a mole or chorionepithelioma may be found very occasionally in cases of severe toxæmia. It has already been mentioned that in exceptional instances the hormone level in a normal pregnancy may reach values which usually indicate the presence of a mole or chorionepithelioma. Finally, the Aschheim-Zondek reaction may remain positive for weeks or even months after expulsion of a mole, and in such cases lutein cysts are often found in which the hormone is probably stored. As long as these points are taken into due consideration, it can be accepted as a general rule that, as soon as hormone in amounts of over 50,000 to 100,000 mouse units per litre are found, the presence of a mole or a chorionepithelioma is extremely probable.

When a patient with hydatidiform mole is being followed up with the purpose of detecting, as early as possible, the development of a chorionepithelioma, the actual amount of hormone present is perhaps not so important as the rise or fall of the hormone titre. The fact that the response to the Aschheim-Zondek test with undiluted urine remains positive even for several months after expulsion of a mole would perhaps not justify a surgical procedure when no clinical symptoms or signs are present. When dilution tests, however, reveal at first a fall and later a rise of the titre, action should not be delayed. Which attitude should the surgeon take when such results of the biological tests are obtained? It has to be stated that the clinical examination may be either completely negative or even misleading. An enlarged uterus may be found or some kind of adnexal tumour be suspected; but it is known that *corpus luteum* cysts, so often associated with moles or chorionepitheliomata, account not infrequently for such findings, and that it often takes some months before the uterus or the ovaries regain their normal size. As in the case presented, even an endoscopic inspection of the cavity of the uterus may not reveal the presence of a tumour.

The histological examination may fail to give a definite result for two reasons. First, the tumour may be inaccessible to a curette. W. A. Scott[1] has reported on two such cases. In both of them the clinical examination and the curettage revealed no abnormality, although in one a metastasis of the skin was found. In both cases the chorionepithelioma, the presence of which was suggested by the Aschheim-Zondek test, was found, after total hysterectomy, in the middle of the uterine wall, covered by endometrium and a thin muscular layer. Even in the case presented here, in which the tumour reached the lumen of the uterus, a curettage, which had to be carried out cautiously, did not produce suitable material for histological diagnosis.

The second reason why a histological examination may not result in a definite diagnosis lies in the difficulty of such a diagnosis. Ehrhardt and Bureck[2] report on a case in which the microscopic sections of several scrapings during a period of over six months were examined by a number of well-known pathologists, none of whom were able to arrive at a definite diagnosis. As eight months had elapsed before a histological diagnosis of chorionepithelioma was secured, it was found at operation that the tumour had already spread into the pelvic tissue and complete removal was no longer possible. Death occurred a short time later from metastases of the brain. In this case the response to the Aschheim-Zondek test had become negative five weeks after expulsion of the mole; but already, three weeks later, the reaction was positive again and remained so during the following period. Total hysterectomy had been suggested as early as eight weeks after expulsion of the mole. This patient was a very young woman. The mole was passed during her first pregnancy, and she desired to have children. The clinical examination revealing no abnormality, and the histological findings being negative or at least uncertain, the operation was postponed, in spite of the result of the Aschheim-Zondek test, until a complete removal of the tumour was no longer possible.

In the case presented here the decision whether to perform hysterectomy or not was perhaps not quite so difficult. The few clinical signs present were certainly no indication for a major operation, as they could well have been due to

a lutein cyst, such as was actually found at operation. The knowledge, however, of the cases referred to previously was a definite advantage, and the decision was made easier by the fact that the patient had already two healthy children. The finding at operation justified the decision to perform a total hysterectomy, and although the recovery of the patient was somewhat delayed, she is now in good health. It is interesting to note that the response to the Aschheim-Zondek test, even with undiluted urine, was already negative eight days after the operation, and it has remained so since then.

### Conclusions.

Conclusions which have to be drawn from the case presented herein and the cases referred to are as follows. Each case of hydatidiform mole should be followed up by the performance of an Aschheim-Zondek test at regular intervals. Although only 5% of patients with a hydatidiform mole can be expected to develop chorionepithelioma, the collection and sending of the urine to a suitable laboratory causes so little disturbance to the patient and to the medical practitioner that it is certainly worth while. Secondly, on the advice of a pathologist, who is aware of the possible fallacies of this test, total hysterectomy should be performed in spite of negative or indefinite results of clinical or histological examinations.

### Summary.

This paper reports a case in which, after expulsion of a hydatidiform mole, a typical fall and rise of the hormone titre in the urine occurred, but in which a diagnosis of the developing chorionepithelioma was not possible either by clinical or by histological examination.

The significance of the Aschheim-Zondek test in its various forms for the diagnosis of normal pregnancy, hydatidiform mole and chorionepithelioma is discussed, and certain conclusions are drawn from the case presented and from some others reported in the literature.

### References.

(1) W. A. Scott: *American Journal of Obstetrics and Gynecology*, Volume XXXVIII, 1939, page 824.

(2) K. Ehrhardt and P. Bureck: *"Die hormonalen Grundlagen beim Chorionepitheliom und ihre diagnostische Bedeutung". Zeitschrift für Geburtshülfe und Gynäkologie*, Volume CXIX, 1939, page 133.

## LARVA MIGRANS OR MYIASIS LINEARIS TREATED BY DIATHERMY.

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THE following case of *larva migrans* or *myiasis linearis* is of interest, not for the diagnosis, but because, so far as I have been able to discover, the treatment which brought about a rapid cure is not mentioned in the literature upon the subject.

FIGURE I.
Second day of treatment.

When the patient was referred to me the lesion was of about two months' duration. The area involved was the shoulder, back and front, with extension into the axilla. There were numerous non-bifurcating burrows, which were about the size of number 4 catgut; the length of the burrows straightened out was up to two feet, and the advance was about one inch per day. Secondary infection due to the intolerable itching and consequent scratching had resulted in a pustular dermatitis, which made it difficult in some instances to find the advancing tip.

Treatment by freezing with carbon dioxide snow or ethyl chloride did not appeal to me, so I used the needle point of my diathermy apparatus, led from an oudin, with one-sixteenth of an inch spark, and worked the switch with my thumb for the sake of rapidity. Provided the spark was in the right spot the relief was immediate. When the first photograph was taken the man had been relieved of the worst of the irritation and the condition was drying up. The time of treatment was seven days; there was a period of five days between the first and second photographs. In all there were about 25 burrows, apart from doubtful ones.

FIGURE II.
Eighth day of treatment.

This is the first time I have seen this lesion in this district. The man came from Cairns. I did not try carbon dioxide snow, but I did try ethyl chloride on two commencing burrows; however, they were advancing the next day, so the patient asked me to return to the oudin. He was usually able to point to the irritating spot.

# Reviews.

## PROGRESS IN ANÆSTHESIA AND ANALGESIA.

A THIRD edition of "Recent Advances in Anæsthesia and Analgesia" has been necessary after a period of only three years.[1] This has been published at a time very opportune for those members of the medical profession who are now in the army and who may be called upon to administer anæsthetics without having much previous experience of modern methods.

The book has been extensively revised and has been increased in size to the extent of forty-nine pages. The general lay-out remains unchanged, but some of the sections have been entirely rewritten. A very extensive bibliography is placed at the end of each chapter. The author has not used the "Harvard System" for references, as he considers that the older method makes the text easier to read and that the original papers may be traced more easily and quickly; with this we agree.

Although there are comparatively few new drugs described since the previous edition, there has been much research into the physiological action of others that have been introduced in the last five years and investigations have been made into the best methods for their administration. Emphasis is laid on methods which are practical and safe and which have been thoroughly tested.

[1] "Recent Advances in Anæsthesia and Analgesia (including Oxygen Therapy)", by C. L. Hewer, M.B., B.S., D.A. (R.C.P. and S., England); Third Edition; 1939. London: J. and A. Churchill Limited. Large crown 8vo, pp. 344, with 132 illustrations. Price: 15s. net.

The opening section on theoretical aspects of inhalation anæsthesia is well thought out and succinct. The Crampton test is fully explained and recommended as the most reliable guide to the patient's general condition. In the chapter on premedication the author discusses very fairly the pros and cons of the many different drugs and explains their advantages and disadvantages. There is a very extensive list of references for those who wish to investigate the subject further.

The short chapter on nitrous oxide and the hydrocarbon gases contains a large amount of information in a very small space; half of this chapter is concerned with cyclopropane. Its many advantages are discussed and it is suggested that "washing out" of nitrogen from the circuit accounts for the occasional occurrence of pulmonary collapse; helium may be used to replace the nitrogen, as it is also an inert gas. Helium has a very low density, and on account of this property has been found to be of great temporary value in respiratory obstruction before the cause can be removed.

The section on modern apparatus for the administration of "gas" anæsthetics is most comprehensive. One illustration, however, that of the controls of the McKesson Model G apparatus, is hardly well chosen, as this machine has been superseded by a number of later and better models. The artificial airways recommended are those of Guedel and Waters, as they withstand the test of causing no retching in a conscious patient. No mention is made of Leech's gasway, which is specially useful when carbon dioxide absorption methods are used for patients who are edentulous and in whom it is difficult to obtain a gas-tight fitting face-piece. The gasway may also be often used instead of an endotracheal tube.

The explosion risk in anæsthesia is considered fully, and suggestions are made concerning the electrical switch gear in operating theatres. A still better method has been introduced in some modern operating theatres by having all the switches outside the theatre and using screw contact lamps only instead of the usual bayonet joint type which is found in most British installations. Anæsthesia induced by intravenous injection has proved very useful in many short operations, but the author refers to an investigation made in the principal hospitals of the Union of South Africa, where it was found that the mortality from "Evipan" ranked next to chloroform in danger, with a mortality rate of 0·14%. It is also stated that at the present time it is impossible to say how prolonged administration of the barbiturates compares with inhalation anæsthesia, and that the method should not be attempted by any but an experienced anæsthetist. The advantages and also the mortality of spinal analgesia are fairly discussed and the view is expressed that spinal analgesia employed in suitable cases has a greater immediate mortality than general anæsthesia, but that the total morbidity is not increased owing to the protection from operative shock which it confers. The original method advocated by Howard Jones for the use of light solutions of "Percaine" is deemed essentially sound, and the modifications suggested up to the present time afford no appreciable advantages, except possibly Lake's technique. The list of drugs recommended to combat fall in blood pressure in spinal analgesia does not include the mixture of ephedrine and pituitary extract advocated by Wesley Bourne.

In the section devoted to collapse and resuscitation it is emphasized that time is the all-important factor in the treatment of primary cardiac failure. Intraarterial perfusion is advocated in certain cases, the chief aim of this proceeding being to maintain a suitable intracoronary pressure, which is now recognized as being essential to the maintenance of the heart beat. The vexed question of *status lymphaticus* is debated, and the recommendation is made that the best way of avoiding primary cardiac failure from *status lymphaticus* is to eschew the use for children of chloroform or any mixture containing it.

The article on anæsthesia in thyreoid surgery is entirely rewritten and is an excellent essay, as one would expect from Langton Hewer, who is a recognized authority on the subject. The technique which he prefers is given in detail and much valuable information is included in this chapter. The importance of auricular fibrillation is emphasized; it is shown to increase the operative risk considerably. In the author's practice, among 1,000 consecutive toxic goitre patients 105 exhibited this feature, and among this group the number of deaths within seven days of operation was 5 (4·7%). Among the remaining 894 patients without auricular fibrillation the total operative mortality was 8 (0·9%). He does not consider that the estimation of the basal metabolic rate is of much advantage, except that it may assist in determining the "Avertin" dosage and also that of the oxygen percentage. The estimation may badly upset a critically ill patient. A warning is given as to the dangers of using adrenaline for thyreotoxic patients, and when using "Avertin"; some surgeons make a test beforehand by injecting a small dose and noting the rise in pulse rate. The oxygen tent is suggested as a preventive for post-operative thyreoid crises.

Anæsthesia in obstetrics is reviewed very fully, and references are given of twenty-four drugs which have been used. The author's preference is for nitrous oxide and oxygen when an anæsthetist is available; when this is impossible he gives second place to nitrous oxide and air. Of the simple methods, he suggests that oral administration of "Pentothal sodium" is the most successful. He considers that midwives should not be allowed to use chloroform capsules and that it is indeed paradoxical that a drug abandoned by expert anæsthetists owing to its toxicity, should be recommended for use by unqualified persons.

The other sections concerning anæsthesia in thoracic surgery, in abdominal surgery, anæsthetic sequelæ and oxygen therapy are full of information and sound common sense.

The book is printed in good type and arranged for easy reading; the illustrations are numerous, clear and adjacent to the text. This is a sound practical book, which should prove most useful, not only to anæsthetist and surgeon, but to the general practitioner and house surgeon.

## ANTENATAL AND POSTNATAL CARE.

IN the third edition of "Antenatal and Postnatal Care", by Francis J. Browne, there are many new illustrations and two new chapters have been added.[1] The first edition of this book was published in 1935, the second in 1937, and the third in 1939. In the preface the author states that "although less than two years have passed since the issue of the second edition, the book has again been thoroughly revised".

One of the new chapters, dealing with heredity, contains an account of Mendelism and its bearings on the inheritance of morbid characters in human families; the other, on "Unsuccessful Pregnancy", includes with additions the matter previously written on habitual abortion. The sections on the remote prognosis of the toxæmias of pregnancy have been rewritten in the light of the knowledge gained from the twelve-year follow-up by Dr. Gladys Dodds and the author of the patients seen since 1926 in the obstetric unit, University College Hospital.

The chapter on "The Anæmias of Pregnancy" has been revised and almost entirely rewritten; and the chapter on "The Uses and Value of Radiology in Obstetrics" has also been revised. In this chapter, written by Dr. R. W. A. Salmond, special attention has been given to modern methods of pelvimetry, and an account of the precision stereoscope of Caldwell and Moloy is included.

The addition of this new material and the revisions mentioned add to the value of this excellent book. To those practitioners who are familiar with the earlier editions, there will be no need to stress the value of the present edition. For the information of those who are not familiar with the earlier editions, we may say that the author discusses every aspect of antenatal care, including the examination of the patient, the diagnosis of early pregnancy, the hygiene of pregnancy, the influence of the emotions upon pregnancy and parturition; maturity and postmaturity; multiple pregnancy (including the Dionne quintuplets); abnormalities in presentations and positions and in quantity of amniotic fluid; hæmorrhage early in pregnancy. There are excellent chapters on ante-partum hæmorrhage, contracted pelvis and disproportion, the toxæmias and the common diseases and disorders of the various systems, digestive, circulatory, respiratory and nervous, and diseases of the ductless glands, the diseases of the urinary tract, skin, venereal diseases and postnatal care. Also included are "Hints to Expectant Mothers" and a list of various diets.

We can strongly recommend this book of some 600 pages to all those who practise obstetrics, whether as general practitioners or specialists, for, in our opinion, it gives an excellent and adequate account of all the common problems met with in antenatal work. The various conditions are dealt with in a sound, concise, judicial manner, and it is an easy book to read. Altogether we have nothing but praise for this most useful addition to obstetric literature.

[1] "Antenatal and Postnatal Care", by F. J. Browne, M.D., D.Sc., F.R.C.S., F.R.C.O.G.; Third Edition; 1939. London: J. and A. Churchill Limited. Demy 8vo, pp. 640, with illustrations. Price: 21s. net.

The Medical Journal of Australia

SATURDAY, OCTOBER 19, 1940.

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## THE NATIONAL HEALTH AND MEDICAL RESEARCH COUNCIL.

A LEADING article was published in *The British Medical Journal* not so very long ago dealing with the "black-out in intellectual Europe" occasioned by the war. The article was concerned with a report of the activities of the Rockefeller Foundation; and reference was made to the "alarming" consequences to the intellectual life of America that would follow the suspension of the fundamental activities of the universities and laboratories of Europe, because of war exhaustion or chaos. The danger of an intellectual black-out has to be faced by the British Empire in this time of national stress; and all thinking people will agree that every possible step must be taken to prevent such a calamity, provided such steps do not place the commonwealth in jeopardy. The intellectual life of medicine has a value apart from its mere intellectuality; it produces ideas capable of being translated into action that will benefit the life of man. To the followers of British medicine, therefore, and on those who have power to mould its destiny falls the task of keeping the light burning though many other lights round it be dimmed. Australia's share in this task is the greater because, though fully involved, she is far from the centre of the turmoil and has not suffered so violent an upheaval as the Motherland. In these circumstances the report of the eighth session of the National Health and Medical Research Council, held at Canberra on May 22 and 23, 1940, has an added significance.

In his opening address to the Council the Honourable H. V. C. Thorby, Minister for Health, said that there were several matters on which he hoped the members of the Council would give him their best advice. One was in connexion with the desirability of securing complete uniformity throughout Australia in the medical profession. Another was the need to utilize broadcasting to a much greater extent to inform people of the important developments regarding health, particularly the prevention of disease. It was his ambition to see the whole of the professions organized on an Australian-wide basis, without any recognition of State boundaries. The Minister asked for the considered advice of the Council in connexion with the possibilities of developing a campaign against tuberculosis, hydatids, leprosy, venereal disease and other contagious diseases. He realized that the present was not the time to engage in expensive campaigns, but at the same time the national health had to be protected, for prevention was much more effective and much more economical than cure. As reported in a previous issue, the Minister added that he was anxious to cooperate with the Council in every possible way to do the utmost to eradicate tuberculosis. From these remarks we may conclude that, if the Commonwealth Minister for Health can help it, there will be no intellectual black-out in the activities of Australian medicine within the sphere of the National Health and Medical Research Council's activities.

The report is a good demonstration of the dual activities of the Council. Both public health and research had their places on the agenda paper and, as would be expected, these aspects sometimes overlapped. The report of the meeting does not give a clear idea of discussions—much space is devoted to a review of public health development (international, Commonwealth and State) and to the activities of the Commonwealth X-Ray and Radium Laboratory, and reviews or reports on such subjects as national fitness, nutrition and research in tuberculosis, to mention a few, receive but scant mention. We propose, therefore, to enumerate the subjects discussed and to indicate the steps taken in regard to each. First, applications for grants in aid of research were considered and sums of money totalling nearly £6,000 were earmarked for various applicants. Some grants were renewals, some were additional to sums already being received, and some were for new investigations. The range of subjects is wide, and many of the renewal grants were made to authors who have already published in this journal the results of some of their investigations. It is noteworthy that no new grant is mentioned for work in tuberculosis. On the other hand, particular interest centres round a systematic study that is being made of the health of a group of children in the Adelaide hills; readers, we hope, will hear more of this later on. Public health under war conditions was discussed and a statement was made on the standardization of alkaloids and other active principles and of vitamins *et cetera*. It was resolved, in view of the national importance and urgency of the work, that the Council should provide a sum of £1,200 as a research grant to finance research into the active principles of medicinal plants grown under Australian conditions, or any others which might be found desirable. The report of the fourth session of the Commonwealth Council for National Fitness was submitted and after discussion the Council adopted a resolution assuring the Minister that the full cooperation and practical assistance of the Council and of the several health departments would be available. The report of the third meeting of the nutrition committee was submitted by Dr. F. W. Clements, who also gave an outline of the work being carried out in the

nutrition investigations. This subject, together with the minimum standards for medical and dental examination of school children, was, we are told, discussed at length. This information is rather meagre, and it is difficult to grasp the full significance of the motion that was carried in connexion with it:

> The Council having in view the transient state of knowledge regarding physiological and nutritional norms, views with concern the growing tendency of commercial organizations to advocate the use of proprietary preparations by unjustifiable propaganda expressed in pseudo-scientific language, or by the use of the findings of scientific investigations, when quoted outside their appropriate context.

The discussion by the Council on tuberculosis was mentioned in the issue of September 14, 1940, and need not be referred to again. In view of the reported increase in the number of cases of venereal diseases it was resolved that the subject should be a major one for consideration at the next meeting of the Council, and that a preliminary session of medical officers of the several States engaged in the control and treatment of these diseases should be held to afford them an opportunity for the exchange of opinions and experiences. During a discussion on public health education, Dr. E. Sydney Morris, Director-General of Public Health in New South Wales, stated that he had issued circulars to all broadcasting stations suggesting that short health talks might be included in their programmes. It was resolved that each State representative should undertake to make an attempt to secure publicity for recorded talks on public health matters and report his experience at the next meeting. In his opening address the Minister, as already stated, had entered a plea for the greater utilization of broadcasting; he also expressed his gratification at the arrangements made for the broadcasting of health talks by the B.M.A. Spokesman over the national network. Though it is not so stated, we cannot doubt that there will be no request in general terms to the commercial broadcasting stations, but that suggestions will be made in regard to the selection of speakers and subjects where no arrangements already exist for this sort of session. In regard to leprosy, Sir Raphael Cilento indicated the progress of the survey in Queensland that had been interrupted owing to the illness of the investigator. Arrangements were made for the continuance of the survey, and Dr. R. C. E. Atkinson, of Western Australia, made a statement setting out the progress of the survey in that State. No other information regarding leprosy is given. A discussion was held on the subject of cerebro-spinal meningitis. The only outcome is to be the publication of an assurance that the Council and all health departments are "very closely watching the situation of this and every epidemic disease". All relevant data are to be collected so that there shall be available "up-to-date information, covering the whole position both as regards diagnosis, treatment and control of each of the major diseases likely to be of epidemic importance under war or post-war conditions". Once this information is available, the medical profession will be happy if it knows that there is a liaison between the Council and the Australian Army Medical Corps authorities.

The National Health and Medical Research Council is making an effort to keep the light of science burning at a time when it is threatened with extinction; organized medicine throughout Australia must follow its example, but with more energy than is displayed in this somewhat cold report of the Council's activities.

# Current Comment.

## THE VISCERO-SPINAL SYNDROME.

IT is well known that such people as chiropractors and osteopaths sometimes achieve dramatic success in the treatment of functional disorders of the viscera when legitimate methods have failed. This is usually ascribed to the psychical influence of the treatment. But is the psychical effect the only one? May there not be some hitherto unrecognized connexion between the disordered viscus and some spinal abnormality, correction of which effects a cure? Neville T. Ussher is one who believes that various sensory and visceral disorders can be eliminated by the correction of spinal deformity or the treatment of abnormalities in adjacent structures.[1] He describes what he terms the "viscerospinal syndrome", a "new concept of visceromotor and sensory changes in relation to deranged spinal structures". He suggests that afferent stimuli arising in the skin, the dorsal muscles or the articulations of the vertebral column, are conveyed to the cord by the dorsal roots and out by the white *rami communicantes* through the sympathetic ganglia and on again by sympathetic efferent fibres to the viscera, skin or muscle, producing visceral spasm or hyperperistalsis, cutaneous hyperæsthesia, or spasm of skeletal muscles. He points out that this conception pictures a reversal of the process of the origin of pain in a viscus and its "being referred to somatic or skeletal structures". He proceeds to discuss the application of his conception to the treatment of functional disorders at various levels. He mentions that orthopædic surgeons "have repeatedly demonstrated that pain in the occiput and posterior auricular regions may be related to cervical scoliosis and myositis involving the cervical and extreme upper dorsal muscle groups"; but he remarks that pain in the areas of distribution of the sphenopalatine and Vidian nerves may also be caused by these disorders. He quotes Vail's description of Vidian neuralgia as a "sharp deep pain in the root of the nose radiating in, about, and behind the eye, over the temple to the ear and the mastoid process to the back of the head and neck, and in severe cases passing into the shoulders and arms". One of Ussher's patients, suffering from persistent pain in the upper jaw and temporo-mandibular joint, was cured by the correction of scoliosis and the application of massage and infra-red radiation to spastic tender cervical muscles.

Ussher asserts that asthma may be caused by spinal abnormalities, and he quotes a series of cases in support of his contention. His treatment consists in postural exercises, massage, infra-red radiation and correction of deformity by such measures as raising the heel of a shoe and so forth. He suggests that the success sometimes achieved by osteopaths in the treatment of asthma results from relaxation of the spastic muscles.

In discussing the possibility of the involvement of the heart in the "viscerospinal syndrome", he points out that the sympathetic innervation of the heart and its vessels is connected with the cervical and upper four or five thoracic ganglia. He goes on to say:

> Our clinical observations . . . suggest that in some cases involvement of the parietal structures (skin, intercostal nerves, intercostal muscles) of the upper dorsal segments of the body may be intimately associated with the development of certain cardiac arrhythmias or changes in the coronary circulation. That this assumption seems bold and unorthodox I cannot deny, but it is consistent with observations of the viscerospinal syndrome in other segmental areas of the body.

[1] *Annals of Internal Medicine*, May, 1940.

He describes one case of cardiac pain relieved by manipulation; but there seems to be doubt as to the true nature of the pain.

According to Ussher, various disorders of the alimentary tract, such as œsophageal spasm, pylorospasm, hyperperistalsis and chronic constipation, may be due to spinal abnormalities. He describes the case of one young man who had constipation and pain in the right iliac region and who recovered completely when his scoliosis was corrected by the elevation of one heel.

He goes on to record the cases of a woman who suffered from frequency of micturition and dysuria, and a man who suffered from pain in the left flank and lumbar region due to spasticity of the ureter, both of whom recovered completely on the correction of spinal deformities.

In a general discussion of the "viscerospinal syndrome", Ussher refers among other things to the suggestion that any benefit obtained by the patient from manipulative treatment or irradiation is purely psychical. He admits the existence of the psychical element, but states that psychotherapy and sedation "have been repeatedly eliminated as being of minor importance in a given case once the viscerospinal syndrome is definitely established". In the course of his investigation endeavours were made to take the patient's attention away from the real therapeutic procedures. "As a matter of fact the difficulty has often been to persuade the patient that such a small item as a heel correction, or simple exercises for a scoliosis has any connection with his cure."

Ussher's work has apparently been carefully done. He has done his best always to find the cause of the patient's trouble and he has not made any sweeping statements to the effect that all functional visceral disorders have their origin in spinal deformity. He has made out a good case for the "viscerospinal syndrome"—good enough at any rate to encourage others to investigate the truth of his assertions. It would be foolish to deny categorically that there was any element of truth in them.

## TOMOGRAPHY AND KYMOGRAPHY.

The last few years have seen several valuable additions to the equipment of the clinical radiologist. Of these by far the most important has been the photofluorograph, which makes miniature X-ray photographs and is effecting a revolution in the epidemiology of tuberculosis. Photofluorography was the subject of "Current Comment" in this journal on October 21, 1939, and its uses are now quite widely appreciated. Two other important inventions of recent years which appear to have escaped very general notice are the tomograph and the kymograph.

The tomograph is an instrument for making X-ray pictures of slices of the human body, so that deeply seated structures or small lesions may be clearly photographed in outline even though they lie in the path of shadows cast by larger or denser structures or lesions. For instance, a cavity in the lung, which is not distinctly visible in an ordinary skiagram because of an overlying pleural effusion or because the collar-bone and ribs overlie it, may be clearly represented. Tomography is effected by means of an arrangement whereby the X-ray tube is moved through an arc of a circle during the exposure while the film carrier, which is connected to the tube by an adjustable lever, moves with it but in an opposite sense. The fulcrum of the lever is adjusted so as to be in the plane which it is desired to examine. Hence, throughout the exposure shadows of objects in the selected plane fall on the same part of the film and are "in focus", while the shadows of objects in other planes do not and are blurred. Complicated and costly machinery is necessary for theoretically perfect tomography; but simpler apparatus which gives very good results may be easily and cheaply constructed. The value of such an apparatus needs no emphasis, although even the busy general radiologist would need it infrequently, for such purposes as the minute examination of joints, of the vertebral bodies, of the walls of cysts and the like. The chief application, however, has been as an aid to clinical judgement in the surgery of tuberculous cavities, and in a forthcoming issue we hope to review a new book on tomography, almost wholly devoted to its application to the chest.

The kymograph is an instrument for delineating the motion of the various "borders" of the heart and of the great vessels and related structures during systole and diastole. By its aid it is possible to see whether there is infarction and consequently loss of contractility in any of the parts of the heart which can be projected to the periphery of its shadow, or to determine whether tumours of the mediastinum are pulsatile or shaken by the pulsation of the heart. The essential part of the kymograph is a metal shutter which is the same size as the X-ray film and placed close to it so as to screen it from the rays during the exposure. The shutter is not complete, being interrupted by a series of very narrow horizontal slits extending throughout its whole breadth and regularly arranged at a distance of about one centimetre from one another throughout its whole length. During the exposure the shutter moves at uniform speed in a vertical direction through a distance equal to the distance between two slits. The length of the exposure is usually equivalent to some two or three or four cardiac cycles. Thus when the film is developed the outline of the heart and mediastinum is seen to be wavy. The amplitude and appearance of the waves vary characteristically according to whether they represent the shadows of atria, of ventricles or of vessels in motion.

In this country it would appear that tomography and kymography are not yet made use of as they could be in clinical medicine, and for the most part the instruments are still toys in the hands of a few radiologists of a mechanical turn of mind.

## THE EARLY DIAGNOSIS OF CHORIONEPITHELIOMA.

The paper by Dr. W. G. Cuscaden and Dr. H. F. Bettinger, published in this issue, is of much more than casual interest. Chorionepithelioma is so insidious and fatal a malady that any means that may be used to discover it while it is still sufficiently localized and small enough to be removed should be welcomed by obstetricians and gynæcologists. The Aschheim-Zondek test has for some years been recognized as one method by which chorionepithelioma may be diagnosed in its early stages. Curiously enough, references in Australian medical literature to the use of the test for this purpose have been scanty. One of the few references appears in The Medical Journal of Australia of October 6, 1934, when Dr. C. Gammie is reported as having discussed the utility of the Aschheim-Zondek test at a clinical meeting of the New South Wales Branch of the British Medical Association in July of that year. In the case reported by Dr. Gammie a woman had been delivered of a hydatid mole and the Aschheim-Zondek test was to be undertaken on account of the possible occurrence later on of chorionepithelioma. Nothing beyond these facts was stated. It should perhaps be pointed out that during recent years extensive surgical measures have been advocated for cases in which a hydatid mole has been expelled or removed from the uterus. We are told in the "Combined Textbook of Obstetrics and Gynæcology", written by Munro Kerr and others, that fear of malignant sequelæ has encouraged supravaginal hysterectomy with the mole *in situ* as appropriate treatment in women over forty years of age, and the authors are in agreement with this view. Certain clinicians have advocated hysterectomy in all cases. Others have used abdominal or vaginal hysterotomy for the emptying of the uterine contents, and have claimed that by this means the uterus may be completely emptied of fragments of mole under direct vision. It does not appear that the number of recurrences justifies any of these measures. The discussion by Dr. Cuscaden and Dr. Bettinger is stimulating and should leave no doubt in the mind of the clinician as to what he should do after a patient has been delivered of a hydatid mole.

# Abstracts from Medical Literature.

## OPHTHALMOLOGY.

### Disease of the Optic Nerves in Post-Vaccinal Encephalomyelitis.

F. von Herrenschwand (*Klinische Monatsblätter für Augenheilkunde*, June, 1939) reviews recent reports on post-vaccinal encephalomyelitis and describes several which came under his notice. Occasionally only palsies of the extraocular muscles have been described as causing transient diplopia and ending in complete recovery. Most authors describe the ophthalmoscopic changes of acute retrobulbar neuritis with much swelling of the disks and a central scotoma. This condition comes on rapidly usually between the fifth and fourteenth days after vaccination. Recovery is usually rapid. In a few cases blindness from optic atrophy has been permanent. Histologically the lesions in the optic nerves closely resemble those of disseminated sclerosis with numerous circumscribed plaques of inflammation, varying in size, situated in the perivascular lymph spaces and extending into the adjacent connective tissue and into the vessel walls. They consist chiefly of numerous enlarged lymphocytes, connective tissue cells and glial cells.

### The Gas Mask and the Correction of Ametropia.

Cot, Moynier, Genaud and Robert (*La Presse Médicale*, September 2, 1939) conducted investigations regarding the safest method of wearing glasses under masks. This is a matter of great importance, as many civilians are incapable of carrying on if deprived of their glasses or of their vision by smeared glasses. Their lot is worse if their spectacles render their masks only partially gas-tight. The various methods for correcting ametropia are glasses with arms of a special design attached to the mask, but also fit for wear without a mask in normal times, corrective glasses replacing the eye-piece disks of the mask, or corrective glasses fixed to the inside of the mask. Various masks were tried for an hour in atmospheres of benzyl bromide and of diphenyl-amino chlorarsine, and also in a cold room at 4° C. Glasses with special frames hurt the nose, were apt to push the mask forwards, and were not gas-tight. The last-named defect was lessened by lateral support, as in *pince-nez* and by the use of arms of elastic fabric. Then the metal arms were replaced by an elastic band fastened behind the head. In the front there was a leather mask with two openings bordered by metallic rings. At one point on the inside of these rings was soldered a metal frame to take the lenses. The frame of the glass and the metallic ring formed a sharp angle opening outwards so that the glasses were in the same plane and their axes parallel to the binocular axis when the mask was in position. The eye-piece disks were deteriorated rapidly by the anti-moisture preparation and the fit was not gas-tight. These defects were removed by replacing the leather mask with air-tight fabric and very thin canvas, as used for balloons. Then the eye-piece disks of masks were replaced with corrective lenses, 40 millimetres in diameter. This was satisfactory in all respects but the need for outside aid in attaching this appliance. The authors discuss Manganaro and Duguet's designs for fixing correcting lenses inside masks. These and a compound design proved to be unsatisfactory. They then worked out a new and very simple appliance. The correcting lenses were set in metal rings which were attached by either simple soldering or a slide-block of variable length at one point of their circumference to a metal guard which was introduced into the groove of each eyepiece disk of the mask. The angle formed by the guard and the corresponding frame was open inside and about 15°. This appliance could be adapted to all masks distributed to the civil population, especially to the "national mask". To ensure that glasses were on a vertical plane the soldering was level with the superior external zone of the groove of the corresponding eye-piece disk. In the case of astigmatism the correcting glass was marked at each end of its horizontal diameter and the point of soldering placed in the superior external section. This appliance was patented in the name of the Ministry of War.

### Sympathetic Ophthalmia.

Sureyya Gördüren and H. Sohr (*Klinische Monatsblätter für Augenheilkunde*, June, 1939) express regret that although sympathetic ophthalmia can be caused by any accidental, operative, or inflammatory injury of the uveal tract, and produce a fairly clear clinical picture, yet the diagnosis cannot be established by means other than enucleation and histological examination of the injured eye. They emphasize the importance of early enucleation of all severe perforating injuries, because once sympathetic ophthalmia has affected the second eye, enucleation of the injured eye is useless. No hard and fast rule can be given as to how long it is safe to postpone enucleation of a suspected eye, but to wait several days should be all that is necessary. Histologically there is thickening of the arterial walls with infiltration of lymphocytes and giant cells, followed later by epithelioid cells. Of 428 eyes enucleated following severe injury the authors found early sympathetic disease histologically in 4·4%, but only half of these presented clinical evidence of its presence. Of all perforating wounds they found sympathetic ophthalmia in 0·25%, and 0·045% followed intraocular operation. In a check-up two years after the patients left hospital no sympathetic ophthalmia was found in the remaining eye in the above series.

## OTO-RHINO-LARYNGOLOGY.

### Gangrene and Infection of the Ear, Nose and Throat Complicating Diabetes Mellitus.

Sol. A. Goldberg (*Archives of Otolaryngology*, July, 1940) reports a case of *diabetes mellitus* associated with gangrene of the intranasal structures, in which recovery occurred; he reviews the literature and discusses clinical manifestations and surgical considerations. The reported case demonstrates the close association between gangrene and infection, the extension of the infection from the soft tissues to the osseous structures by contiguity and the production of acute localized osteomyelitis being shown, as well as the spread of infection to the vascular channels resulting in arteritis, phlebitis, thrombosis, occlusion and gangrene. The literature shows the delayed healing of wounds to be the result of changes in the vascular structures and of poor defensive mechanism. The importance of the role of the latter factor was substantiated in the reported case by the poor cellular reaction, the patient having relative or absolute leucopenia during his stay in hospital. Gangrene limited to the intranasal structures is not invariably fatal. The lesion in that area is in this respect in contrast to that occurring on the superficial aspect of the face and cheeks, where the abundant vascular supply facilitates spread to the venous channels, producing cavernous sinus thrombosis, or to the systemic circulation, producing septicæmia or metastatic abscesses. The prognosis is dependent on many factors—for example, the type of infection, location of the primary lesion, status of the vascular supply, general condition of the patient, and, finally, intelligent conservative treatment.

### Osteomyelitis of the Frontal Bone.

Karsten Kettel (*Archives of Otolaryngology*, April, 1940) discusses the way of approach in the surgical treatment of osteomyelitis of the frontal bone. He is of the opinion that unrestricted access for resection of the frontal and the adjacent parts of the parietal bone, the frontal sinuses, the ethmoid labyrinth, the roof of the orbit and the *lamina cribrosa* is obtained by a coronal incision above the hair line, which permits reflection forward over the face of the scalp covering the forehead. The cicatrix is concealed by the hair, and, as no branches of the facial nerve and no muscles have been cut, and as no tense scars are to be found on the forehead, the cosmetic and mimetic results are ideal.

### Nasal Plethysmometry as a New Test for Sinus Thrombosis.

H. A. E. van Dishoeck (*Archives of Otolaryngology*, April, 1940) describes a new test for sinus thrombosis. It is based on the fact that compression of the healthy jugular vein, the other jugular vein being obstructed, in most cases causes congestion of the wide venous spaces of the nasal turbinates. The swelling can sometimes be detected by anterior rhinoscopic examination; but with a specially constructed nasal plethysmometer it can be demonstrated in every case. Some abnormal conditions in the nose and in the venous connexions between the skull and the neck which may complicate the interpretation of the test are discussed.

### Nasal Osteomata.

A. S. Handousa (*The Journal of Laryngology and Otology*, April, 1940) discusses nasal osteomata and reports a number of cases. Males are more commonly affected than females. Age incidence has been between twelve and fifty-four; the majority of patients have been below twenty-eight years of age. In view of the long time that these newgrowths take before they show themselves, it becomes evident that they are essentially an affection of the bones during their period of growth: the same holds true of osteomata in relation to long bones. Except in one case osteomata have been single. Most probably nasal osteomata stop growth with the cessation of growth of the affected bone, following the same rule as osteomata of the long bones.

Surgical removal is the only method of radical cure. It is carried out when the tumour gives rise to symptoms or complications. Symptomless osteomata in adults can be safely left alone, as they are not likely to grow bigger and give rise to symptoms later or change into sarcomata. Extranasal exploration is the most suitable method, good access being essential. The author ascertains beforehand the exact site of attachment of the osteoma to the affected bone by X-ray investigation. This simplifies the operation and saves time and mutilation, as when the affected bone is cut through slightly beyond the site of attachment the tumour, with its cartilaginous covering and pedicle, is left quite free in its cavity, ready for removal. In that way, too, recurrence is avoided. The cavity left, usually a dilated sinus or group of sinuses, is carefully examined for the presence of pus and the condition of the mucosa, and is dealt with accordingly; suitable intranasal drainage is provided and the wound is closed externally. Unusual bleeding does not take place and so previous ligature of the carotid artery has not been found necessary.

### Radiological Diagnosis of Cancer of the Accessory Sinuses.

GEORGE E. PFAHLER AND JACOB H. VASTINE (*Archives of Otolaryngology*, April, 1940), in a paper dealing with the radiological diagnosis of cancer of the accessory sinuses, conclude that to think of the possibility of cancer of the accessory sinuses is the first essential in making the diagnosis. Most diagnoses are made late, and therefore in most cases the condition is incurable. In such a serious disease every possible means of diagnosis must be utilized. These include the careful taking of the history, thorough clinical observations and a thorough X-ray investigation, with an adequate number of projections and detailed study; finally, a biopsy is essential for early diagnosis. Cancer involving the accessory sinuses varies in its distribution and characteristics according to the types which the authors describe. The treatment and management will also vary with these types. In some cases irradiation alone will give best results. In other types a combination of surgical or electrosurgical measures and irradiation will give best results. Individual consideration is absolutely necessary in each case, and the type of disease and its location, extent and duration especially must be taken into account.

## MEDICINE.

### The Ductless Glands and Peptic Ulcer.

ASHER WINKELSTEIN (*Journal of the Mount Sinai Hospital*, May-June, 1940) discusses a possible relationship between the ductless glands secreting the sex hormones and peptic ulcer. He notes that during pregnancy ulcer symptoms frequently improve or disappear, that there is a large group of patients who experience the onset or exacerbation of a peptic ulcer at the natural or artificial menopause, that peptic ulcer is strikingly predominant in the male sex and in women it is comparatively a mild disease, and that perforation, hæmorrhage and post-operative recurrent ulcers are quite infrequent in women. The author quotes some experimental evidence to show that during œstrus in the dog the secretion from a fundus pouch diminishes considerably and that ulceration about the pouch heals completely. He then states that experimental observations indicate that the anterior pituitary gland (which secretes the lactogenic hormone) may be associated with increased gastric secretion and ulceration, whereas œstrin, possibly with progesterone (causing œstrus), is involved in the healing process during the œstrus. The author suggests that, because œstrin is inhibitory to the anterior pituitary gland, the mildness and infrequency of peptic ulcer in women may be the result of normal pituitary inhibition by œstrin and so hypothecates that peptic ulcer is primarily a pituitary disease in which some increased anterior pituitary secretion leads to peptic ulcer. Androgen and œstrin *plus* progesterone may normally check this hyperactivity and an imbalance may lead to the development of peptic ulcer. The author notes in his own series the large proportion of female patients in whom severe ulcer complications occur at or after the menopause, and he cites this observation as illustrative of an unchecked, uninhibited or hyperactive anterior pituitary gland, with the inhibitory influence of œstrin practically absent. The author treated twenty of his patients in whom ulcer symptoms started coincidentally with the onset of an artificial or natural menopause, with œstrogen therapy in the form of 20,000 international units of "Progynon B" given intramuscularly three times a week for a period of three weeks. Test meals were given and skiagrams were taken before therapy was begun, and vaginal epithelium was studied to ascertain whether the dosage was effective; in some cases a weekly gastric analysis was carried out, in others a test meal was given before and at the end of the period of therapy. Symptomatic improvement during treatment was noted, though there was no notable change in the acidity curves, and in some the clinical improvement persisted for some months. Recurrences were frequent, but were usually quickly relieved by further injections of the hormone. The author observed that the usual nervous symptoms of the menopause (insomnia, dizziness, flushes, constipation) were also benefited with the treatment, but he prefers not to draw any definite conclusion as to whether the improvement noted in his series of cases is attributable to a specific effect on the gastric function or mucosa *per se*, or to a secondary effect brought about by a general symptomatic improvement, that is, relief of the neuro-vascular symptoms of the menopause. He concluded, however, that ulcer symptoms which develop at or about the menopause may be relieved by œstrogen therapy in the majority of cases, and that this form of therapy is worthy of trial in such instances. The author states that the use of androgen, œstrogen and progesterone in the treatment of peptic ulcer in both the female and the male patient awaits further experimental and clinical investigation, and that the clinical and experimental observations he has made require confirmation and further study.

### A New Treatment for Leprosy.

AT the leprosy institution at Chiengmai in North Thailand novel experiments have been made which seem likely to be of great value, according to an "annotation" in *The Lancet* of June 8, 1940. Diphtheria antitoxin was injected into patients during an exacerbation of the disease. This had the effect not only of immediately clearing up the reaction, but also of causing what seemed to be a permanent improvement of the leprous condition. Later, injections of diphtheria formoltoxoid were given, and again encouraging results were reported. Dr. Collier, of the American Presbyterian Mission at Chiengmai, concluded after a survey of four hundred treated patients that in general the activity of the disease was brought to a halt almost immediately and healing began.

### Nephrectomy for the Relief of High Blood Pressure.

H. A. SCHROEDER AND G. W. FISH (*The American Journal of the Medical Sciences*, May, 1940) have followed the progress for many months after operation of seven patients from whom a diseased kidney was removed for the relief of high blood pressure. They show that the removal of a diseased kidney cannot be expected to give the desired relief in all or in many cases. They suggest that the operation should be undertaken only when the blood pressure is known to have become elevated within recent years and is persistently high, when the renal disease is unilateral and of such a nature that the function of the affected kidney is impaired, when it is known from normal results of renal function tests that the other kidney has not been badly damaged, and when retinal arterial changes are absent or minimal.

### Preparation for the Glucose Tolerance Test.

J. W. CONN (*The American Journal of the Medical Sciences*, April, 1940) states that sometimes patients are referred to him for treatment of diabetes whose diminished tolerance for carbohydrate is the result of a deficient intake of carbohydrate. The phenomenon of "hunger diabetes" has been recognized for half a century, but not the importance of its occurrence in minor degree in clinical medicine. In order that glucose tolerance tests should be comparable and capable of true interpretation, the subject should have had an adequate diet for at least several days previously.

### III Effects of Intravenous Injections of Sucrose.

W. A. D. ANDERSON AND W. R. BETHEA (*The Journal of the American Medical Association*, May 18, 1940) describe characteristic and severe lesions which were found in the kidneys of six persons to whom hypertonic solutions of sucrose had been given intravenously. The principal lesions consisted of extreme foamy swelling of the cells lining the convoluted tubules, and death of the cells occasionally occurred. The authors conclude from these findings and from a number of experiments with animals that the administration of large or repeated injections of hypertonic sucrose solution, which is becoming a popular measure for the relief of increased intracranial pressure, is inadvisable.

### Sulphathiazole in Bubonic Plague.

S. S. SOKHEY AND B. B. DIKSHIT (*The Lancet*, June 8, 1940) report that for mice experimentally infected with *Pasteurella pestis* sulphathiazole is a much more effective curative agent than sulphapyridine, and about as good as an effective anti-plague serum.

# Special Articles on Psychiatry in General Practice.

*(Contributed by request.)*

## XVI.

## WAR NEUROSES.

The Great War of 1914-1918 gave a prominence to the neuroses and excited an interest in them which has not waned during the last twenty-one years of uncertain and troubled peace.

Now that we are in the throes of another war, in which fear-inspiring influences will be no whit less than in the previous struggle, the neuroses as seen in war will attract additional attention. Past experience and an increased knowledge of the various phases of these functional conditions should make for a clearer understanding of them than existed in the early days of the Great War.

It is as well to realize that the term war neurosis does not connote some new nervous disorder which has not its counterpart in civilian life. When large bodies of men are engaged in a long and bitter war, neuroses will be seen more frequently, and by the terrifying nature of modern scientific warfare, neurotic manifestations appear in character more acute and severe than in civilian life; but the essential features of the functional disorders remain the same in both peace and war. Moreover, neuroses are not confined to the actual combatants, but occur frequently in training camps and amongst civilians who have not been exposed to bombardment either by bombs or shells.

It is with the acute stages of these functional disorders that I propose to deal. The precipitating cause may be either commotional or emotional shock, or mental and physical exhaustion from prolonged stress and strain. Often there is a combination of all three factors.

### Commotional Shock.

Commotional shock is a condition of concussion following upon the bursting of a high-explosive shell in the immediate vicinity of the soldier or resulting from burial by débris from a shell or mine explosion. There may be no evidence of external injury, though in all probability superficial abrasions or contusions, possibly rupture of the tympanic membranes, may be found. Unconsciousness, varying from a few minutes to several days in duration, generally follows immediately, and the symptoms of *commotio cerebri* as seen in civil life will be found—for example, loss of deep reflexes, general muscular relaxation, pupillary changes, and a weak pulse *et cetera*. There may, however, be no loss of consciousness, but the patient merely appears dazed, shocked, tremulous, and possibly mildly confused. Such symptoms may be only transient. On recovery of consciousness, complete amnesia for the periods immediately before and after the injury will be found. The loss of emotional control, which is commonly seen in emotional shock, is not seen in purely commotional shock. Headache following commotional shock is usually mild or absent in the morning, but tends to appear as the day wears on and fatigue sets in. The fine tremor of the limbs, too, seen in post-concussional conditions, is quite different from the coarse tremulousness of the head and limbs frequently observed in emotional states. Neuroses directly attributable to commotional shock alone were regarded as infrequent in the last war.

A history of having been blown up or buried is commonly given by war neurotics, but closer inquiry usually indicates that the trauma was emotional and not commotional. Statements from patients regarding unconsciousness also must be accepted with due reserve, for the stage of amnesia or stupor, even mildly confused states, are often regarded as "unconsciousness" by them.

### Emotional Shock.

Although acute emotional shock is seen most commonly after the soldier has been shaken by a shell burst or other explosion, it not infrequently manifests itself when he has been removed from the danger area. Often he has been troubled by fears and anxieties for some time previously and the violent explosion merely acts as a precipitating agent for an uncontrollable outburst of emotion. His instinctive reactions to the terror and horror he experiences overwhelm his reason.

Clinically, emotional shock may be followed in the milder cases by a temporary dizziness or slight mental confusion, which tends to pass off after a short rest; in the severer cases there may be stupor or mental excitement in varying degrees.

In the milder stuporose conditions the man appears dazed and apathetic, so that he does not seem to understand what is said to him, and he moves about in a slow and purposeless manner. He shows marked body tremor and is easily startled.

In the severer types the patients lie in a collapsed condition, oblivious to their surroundings. They cannot be roused; but tendon reflexes are either normal or exaggerated, and though pupillary changes may be present, the swallowing reflex is not lost. Recovery sets in gradually or suddenly in a few hours to as many days; but there is amnesia for events during, before and after the actual shock. However, the loss of memory is not absolute as in commotional shock, for the gaps may be filled in later, notably by hypnosis.

The clinical picture in the milder cases of mental excitement is one of fear and anxiety. There is a feeling of tension with general body tremor and "jumpiness". Headache and dizziness are complained of. In the more severe cases the patients are in a state of abject terror. They are confused, disorientated and rush wildly about, babbling, or even screaming incoherently. It is usually necessary to place restraint on such men in order to quieten them, and generally they can be brought into a more collected state of mind, though tremor and apprehension are still evident. The man of neurotic disposition tends to succumb readily to emotional shock.

### Prolonged Stress and Strain.

Physical exhaustion alone is a minor predisposing factor in war neuroses, but when combined with nervous exhaustion from loss of sleep, poor food and monotony, it assumes a more important position.

The earliest stage is seen as simple fatigue, which may be quickly dissipated by a short period of rest and the provision of good food and adequate sleep.

The severer forms appear as a state of mental depression, sometimes accompanied by confusion. There is difficulty in getting off to sleep, the ability to concentrate is impaired, the memory is defective and the man appears physically exhausted.

While emotional shock is regarded as the commonest precipitating factor of the war neuroses, accounting for 70% to 80% of cases, the anxiety states and hysteria are the most frequent manifestations of these disorders.

### Anxiety Neurosis.

The general attitude of the anxiety neurotics is one of suppressed excitement. They are harried by fears and anxieties which find expression in vasomotor or visceral manifestations. They are tremulous and have little emotional control. Headache, giddiness, sweating and palpitation are commonly complained of, and there is general bodily weakness. Insomnia is frequent, and even if sleep is attainable, it is disturbed by dreams, some merely of a worrying nature, but often of the true "battle dream" type, in which memories of terrifying incidents are reproduced or elaborated towards the gruesome side. Not infrequently the dreams are projections from an amnesic stage and may not be recognized by the patient as actual experiences until later revealed by analysis.

Cardio-vascular symptoms, such as tachycardia, diffuse and forceful apex beat, irregularities of rhythm, are common. The cardiac response to effort is exaggerated.

Exophthalmos of varying degree may be seen and may be accompanied by some fullness of the thyreoid gland. The patient tends to brood over his symptoms, and places sinister interpretations on them—for example, his cardio-vascular symptoms suggest to him that he has heart disease, or he may believe that his paroxysms of fear, his insomnia and his inability to concentrate denote insanity. He becomes depressed and demoralized.

### Hysteria.

The hysterical conditions as seen in war reveal the same multiplicity of types as in peace. Functional blindness or deafness, mutism or disorders of motor function occur as the most dramatic hysterical forms, while the muscular and cutaneous hyperæsthesiæ are the most common. A gross body tremor, sometimes accompanied by various tics, is frequently observed. The appearance of hysterical symptoms is usually delayed hours, maybe days, after the event which has precipitated their onset. The functional paralyses, for instance, frequently arise in base hospitals during convalescence from medical as well as surgical conditions, and it is usually the sufferer from some minor complaint who develops a major functional disorder.

In their early stages the conversion neuroses can be successfully attacked by counter-suggestion, by persuasion and by demonstrating clearly to the patient that their basis

is functional, not physical. It is a noteworthy fact that the more incapacitating functional states, for example, hysterical paraplegia, mutism or blindness, have seldom persisted in post-war years. The need for an honourable escape from an intolerable position no longer exists.

### Treatment.

Experience in the last war has shown that prompt treatment is essential to prevent these functional disorders from becoming systematized into a persistent habit of mind. The further the man is removed from the forward area, the less chance there is of early cure.

To the medical man on the spot will fall the task of ensuring that the man's self-confidence is restored as quickly as possible. Reassurance that no physical hurt has been sustained and an appeal to the man's sense of duty will tend to allay his fears. A short rest with his unit, in order to allow the initial shock to settle down, would be advisable; but as early as possible strong efforts should be directed towards persuading the man to view his symptoms in their true perspective and to face up to his difficulties.

In the severer cases and in the treatment of those resistant to simple measures there will be need for more elaborate methods, such as were instituted at various neurological centres in France during 1916 and 1917. Units of this type were situated ten to twelve miles behind the line, with the intention of supplying prompt treatment, of ensuring a measure of security from shell-fire while retaining the suggestion of a forward area. Everything possible was done to encourage an "atmosphere of cure", and the patient was made to feel that all hope was not lost.

A period of rest in bed for three or four days with good food and adequate rest was allowed and then active treatment along definite lines was undertaken. Even during this preliminary resting stage hysterical patients were given strong suggestions as to the curability of their symptoms. Insomnia was dealt with by adequate sedative treatment in order to reestablish the sleep habit. The patients were dealt with individually and each man's case was discussed with him at private interviews. Explanations as to the nature and origin of his symptoms were given, so that he might understand, for instance, why he suffered from tremors, why his heart beat rapidly or why he experienced difficulty in concentration.

In the conversion states the majority of patients responded very readily to treatment by suggestion and persuasion, supplemented when necessary by faradism and remedial exercises. Hypnosis is spoken of very appreciatively by medical men who worked in these neurological centres in France, as a quick and successful means of resolving hysterical manifestations.

As improvement in the patient's condition set in, graduated exercises were added to the daily routine of treatment as a measure of reeducation towards the attainment of fitness. Useful occupations, in which the patient could take an intelligent interest, were also arranged, in order to combat introspective tendencies and consequent mental depression.

The period of hospitalization was made as short as was consistent with return to fitness, and this was usually attained in a matter of weeks. The results of this line of treatment were remarkably good.

A certain number of patients, especially those of marked neuropathic temperament, did not respond to treatment. They had passed out of the acute stage and the neurosis had become fixed. The treatment of this type of patient involves the use of psychotherapy in all its varied forms, and requires much patience and specialized experience on the part of the medical attendant.

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## British Medical Association News.

### SCIENTIFIC.

A MEETING of the New South Wales Branch of the British Medical Association was held on May 23, 1940, at the Royal Prince Alfred Hospital. The meeting took the form of a number of clinical demonstrations by members of the honorary staff of the hospital.

### Mitral Stenosis with Cerebral and Pulmonary Embolism.

DR. LAURENCE HUGHES showed a female patient, aged forty-five years, who had a history of rheumatic fever in childhood and a "heart attack" twelve months prior to the meeting; since then she had been under treatment for her heart condition, but had been able to get about and do her routine house work. Two weeks prior to her admission to hospital the patient wakened from her sleep during the night and found that she was unable to speak. She lost consciousness later and was comatose for two days. When she regained consciousness it was noticed that she had completely lost the use of her right arm and leg and that she could not speak. On her admission to hospital paralysis of the right side of the face, the right arm and the right leg and complete aphasia were present. There were pronounced auricular fibrillation and signs of mitral stenosis. After a month in hospital considerable improvement in the condition of the arm and leg and also in speech had occurred; but the fibrillation was only slowly responding. A month later the patient was very much better in every respect and was allowed up. A few hours later she commenced to vomit and was put back to bed. She then complained of severe pain in the right axilla; she was cyanosed and distressed and had a small hæmoptysis. Râles and a friction rub were heard in the right axilla, and a diagnosis of pulmonary embolism was made. At the same time she again became aphasic and lost the power of the right arm. Fibrillation was again very pronounced. She was critically ill for several days; but her condition gradually improved again in every respect, and she left hospital six weeks later with only slight weakness in the arm and leg and almost complete recovery from the aphasia.

### Mitral Stenosis and Cerebral Embolism.

Dr. Hughes's next patient was a female, aged fifty-two years, who had been treated in hospital three years earlier for coronary occlusion. During the few days prior to her admission to hospital in 1940 she noticed a definite weakness of the right side of the face and right arm. This was followed by a sudden loss of consciousness for a few hours prior to her admission to hospital. On recovering consciousness the patient was unable to speak and seemed "paralysed down the right side". Examination revealed a right-sided hemiplegia involving the face, arm and leg; and the patient was completely aphasic. On examination of the cardio-vascular system auricular fibrillation was noted, together with signs of mitral stenosis. The systolic blood pressure was 150 and the diastolic pressure 110 millimetres of mercury. No abnormality was detected in the urine. The Wassermann test produced no reaction. The subsequent clinical course was one of general diminution of the hemiplegia, and the patient left hospital after ten months with full power in the right leg and only slight weakness in the arm and face. There was very little reduction in the aphasia.

### Carcinoma of the Lung; Infiltration of the Pericardium and External Occlusion of the Left Coronary Artery.

Dr. Hughes next discussed the history of a male patient, aged fifty-three years, who had been admitted to hospital on February 7, 1940; he had had typhoid fever at the age of fifteen years and pleurisy eighteen months prior to the meeting, but no other illnesses. The patient had been in normal good health until a year earlier. Four months prior to the meeting he began to have attacks of breathlessness, mostly at night. They lasted for only a few minutes. Two months earlier he began to notice a fairly persistent wheezing, just as pronounced during the day as at night. He had had a "loose cough" for years, not associated at any time with much sputum. He had lost a considerable amount of weight in the past six months.

On examination it was seen that the respiratory rate was increased. The expansion was slightly less on the right side than on the left. Vocal fremitus and breath sounds were diminished over the whole of the right side of the chest, more so at the base of the right lung; scattered rhonchi were present over the same area. The fingers were clubbed. There were no abnormal findings in the cardio-vascular system, apart from a pronounced pericardial rub. An X-ray examination revealed "some consolidation at both bases, probably pneumonia". The temperature was subnormal. A blood count revealed no abnormality. An electrocardiographic examination resulted in a typical tracing of coronary occlusion.

On February 16, 1940, the dulness at the bases of both lungs was more pronounced and more respiratory distress was present. Aspiration of the thoracic cavity was carried out, and three-quarters of a pint of blood-stained fluid was removed from each side; the condition was regarded as a pulmonary neoplasm.

A post-mortem examination was made on February 23. The lower lobe of the right lung was found to be infiltrated with carcinomatous growth, communicating in its upper part with a bronchus. Metastases were present in the

mediastinal and hilar glands and in the suprarenal gland. The pericardium was infiltrated with carcinomatous growth, which surrounded and occluded the anterior descending branch of the left coronary artery.

### Coronary Thrombosis and Plumbism.

Dr. Hughes finally showed a male patient, a metal worker, aged forty-eight years, who had had lead poisoning three years earlier, but no other illnesses. He had been in his usual health until October 15, 1939, when, while resting, he was seized with a severe pain in the chest, located at the lower end of the manubrium; the pain extended down both arms and to the left shoulder blade. The pain was severe and persistent until it was relieved by morphine. Vomiting was present. No breathlessness was noted, but the patient had a feeling of constriction in the chest. He had previously had slight pain in the chest after vigorous exercise.

On examination the pulse was found to be regular and slow—55 beats per minute; no abnormality was found in the heart or lungs. The systolic blood pressure was 220 and the diastolic pressure 170 millimetres of mercury. Auricular fibrillation occurred three days after his admission to hospital, but persisted only for a couple of days. A series of electrocardiograms revealed a typical coronary occlusion of the anterior type with subsequent auricular fibrillation, nodal rhythm, return to normal rhythm, and late inversion of the $T$ waves. The urine contained a heavy cloud of albumin, a few red cells and hyaline and granular casts; 0·2 milligramme of lead was excreted in twenty-four hours. The blood serum failed to react to the Wassermann test. The urea content of the blood was normal. Punctate basophilia was present.

### Actinomycosis of the Lung.

DR. COTTER HARVEY showed a male patient, aged forty years, a bootmaker, who had been admitted to hospital on January 26, 1940. He had had a swelling and a discharging sinus in the right side for one month. His illness had begun in August, 1939, with stabbing pain in the back; this had been diagnosed as pneumonia and pleurisy. At that time he was put to bed and it was said that he had "fluid in the lung". In September, 1939, he was admitted to hospital. A pocket of pus formed and a swelling appeared in his right side; the pocket of pus was drained by means of a tube and actinomycetes were found in the pus. There had been a discharge from the wound ever since. There was nothing relevant in his previous personal or family history; he had no history of tuberculosis.

On examination the patient was seen to be pale. Examination of the respiratory system revealed diminished movement at the base of the left lung anteriorly; tenderness was present round the area of the sinus. The percussion note was not impaired, but the breath sounds were impaired on the right side. The breathing was vesicular and no râles were present.

Dr. Harvey said that the following types of treatment had been tried without improvement in the patient's condition: the administration of potassium iodide and of Lugol's iodine, and thymol given by mouth and applied locally. At the time of the meeting there was evidence of necrosis of the ninth and tenth ribs, and it seemed that the disease was spreading inexorably. The prognosis therefore had to be regarded as bad. The only treatment could be palliative—namely, incision of swellings which became superficial and caused the patient considerable pain; this procedure had already been carried out five or six times.[1]

### Hæmolytic Anæmia.

DR. T. M. GREENAWAY showed several patients suffering from hæmolytic anæmia, and specimens of enlarged spleens removed from these patients. He also showed blood films showing the typical blood picture of poikilocytosis, anisocytosis, spherocytosis, nucleated erythrocytes and pronounced reticulocytosis. The hæmatology department of the hospital had further cooperated by arranging a demonstration of the corpuscular fragility test. Dr. Greenaway remarked that acholuric familial jaundice was the best-known form of hæmolytic anæmia; and the woman from whom the first specimen was taken presented a typical picture with a history of recurrent jaundice and splenomegaly since childhood. The blood count varied from 3,000,000 erythrocytes to as few as 1,500,000 per cubic millimetre. By no means all patients seen manifested text-book signs and symptoms. In the case of the patient under discussion there was no relevant family history. In fact, from none of the patients shown had anything of importance in the family history been obtained. The term "hæmolytic anæmia" was preferable, since even such cardinal signs as increased erythrocyte fragility were not always present. To illustrate this point Dr. Greenaway showed a young girl, aged thirteen years, who had been admitted to the Ryde District Hospital; at that time the erythrocytes numbered 1,500,000 per cubic millimetre. Her condition gradually improved; but it was not until all investigations had been repeated several times that increased erythrocyte fragility appeared.

Dr. Greenaway said that the response to splenectomy in cases of acholuric familial jaundice was dramatic. Splenectomy should be considered in all cases in which criteria of hæmolysis were present in association with splenomegaly. A successful example of the results of this procedure was provided by a male patient, aged forty-eight years, who had first been seen by Dr. Greenaway on March 28, 1938. At that time his blood picture indicated anæmia and reticulocytosis, and the response to the Van den Bergh test was indirect positive. Splenic enlargement was not detected until some months later. The patient was admitted to the Royal Prince Alfred Hospital, where splenectomy was carried out by Dr. D. McCredie on August 11, 1938. The number of erythrocytes immediately increased and had not been below 4,500,000 per cubic millimetre since October, 1938. One interesting point in the man's progress after operation was commented on by Dr. Greenaway. In December, 1938, enlargement of the cervical and axillary lymph glands occurred, presumably associated with mediastinal involvement, as considerable distress was present. Furthermore, a small pleural effusion was present on the left side. This condition settled down completely with X-ray therapy, and naturally enough it was thought that splenectomy had been performed on a patient suffering from lymphadenoma, in the course of which disease hæmolytic anæmia sometimes occurred. It appeared, however, that such was not the case, as the man had been perfectly well since. Dr. Greenaway offered no explanation for this apparent lymphglandular response to splenectomy. He said that he had seen it again recently after splenectomy in an otherwise straightforward case of thrombocytopenic purpura.

### Disseminated Sclerosis.

Dr. Greenaway then showed two patients suffering from disseminated sclerosis. The history of the first patient, aged thirty-two years, which had commenced ten years earlier, contrasted with that of the other, aged twenty-seven years, whose illness had commenced only fifteen months earlier. Both patients gave a characteristic history of intermittency in the earlier stages, and at the time of the meeting showed diffuse pyramidal involvement with nystagmus, and in the second case speech involvement. Despite the second patient's short history, the widespread involvement, including speech defect, nystagmus and a characteristic bitemporal pallor of the optic disks, made the diagnosis certain.

### Electrocardiographic Demonstration.

DR. KEMPSON MADDOX showed a number of lantern slides illustrating the characters seen during recent and healing infarction of the apex of the left ventricle, and some other conditions simulating those appearances in the electrocardiogram. He pointed out that anterior myocardial infarction, due usually to a blocking of the anterior descending branch of the left coronary artery, produced deformity principally of the first and fourth leads of the cardiogram—the so-called "$Q_1T_4$ pattern". This consisted of an upward deviation of the $R$-$T$ segment in Lead I, combined with varying degrees of $Q$ wave development. Reciprocal changes occurred in Lead III. Later, "cove-plane" or "coronary" $T$ waves made their appearance, and in two or three weeks the deviation of the $R$-$T$ segment disappeared. As a late relic of anterior infarction a negative $T$ wave in Lead I and Lead IV had a diagnostic value, provided they arose from an $R$-$T$ segment having an iso-electric level.

Dr. Maddox went on to discuss posterior myocardial infarction. He said that this was infarction of the posterior basal portion of the left ventricle and adjacent interventricular septum supplied by the circumflex branch of the left coronary artery or by the right coronary artery. In this condition the following abnormalities occurred: (i) Conspicuous $Q$ waves in Leads II and III only ($Q_2$ pattern). (ii) Elevation of the $R$-$T$ segment in Lead III and depression in Lead I ($T_2$ pattern). The $R$-$T$ segment was frequently elevated in Lead II also. This returned to normal in two to four weeks, by which time the $T$ waves in Leads I and III had become of the "cove-plane" type. Later, all that might remain was a "cove-plane" $T$ wave in Lead III. Unless a pronounced $Q_2$ pattern coexisted, this could not be taken as evidence of previous infarction. The $T$ waves in Lead IV were often normal all the time, except for early $R$-$T$ deviation upwards.

Discussing the electrocardiogram in predominant ventricular strain, Dr. Maddox said that significant $T$ wave negativity occurred in conditions producing predominant

[1] Early in July further operation was performed; the ninth and tenth ribs were found to be heavily involved by the disease and were removed.

strain upon one or other ventricle. Careful correlative studies had shown that this occurred regardless of the condition of the coronary arteries. In hypertension these changes in the *T* waves might appear long before there was clinical evidence of myocardial failure. Probably the myocardial fibres were fatigued. An increase in concentration in the cardiac muscle diminished the duration of electrical effect and other factors. These changes in the *T* waves were reversible when the source of strain was removed—for example, after surgical treatment of hypertension or a few days after pulmonary embolism. The changes occurred in congenital heart disease with normal coronary arteries. It was particularly to be noted that the changes in the *T* waves might exist without significant axis deviation. That was rare, however, and left axis deviation preceded *T* wave inversion.

In chronic left ventricular strain the *T* wave in Lead I was negative; it was preceded by an *S-T* segment, originating below the isoelectric level. Reciprocal changes occurred in Lead III. Lead II seemed to depend on whether changes were greater in Lead I or Lead III. This was in contrast with acute coronary occlusion, in which the final direction of *T* waves in Leads I and III was opposite to the direction of *R-T* or *S-T* deviation. Lead IV was variable and of little assistance (the *S-T* interval was often depressed). The extent of the changes had no prognostic significance.

Acute right ventricular strain (acute *cor pulmonale*) was seen shortly after acute pulmonary embolism, which might be confused clinically with coronary occlusion, especially of the posterior basal portion of the left ventricle. It was distinguished by the following characteristics: (i) the *S* wave in Lead I was larger; (ii) the *S-T* depression was less pronounced in Lead I; (iii) the *S-T* elevation was less marked in Lead III; (iv) inversion of the *T* wave occurred; (v) changes disappeared more quickly. Changes were not constantly seen after every pulmonary embolism.

Chronic right ventricular strain (chronic *cor pulmonale*) occurred in conditions of raised pressure in the pulmonary circulation. It was necessary to distinguish carefully pulmonary stenosis, obstructive emphysema, pulmonary arteriosclerosis and mitral stenosis from $Q_3T_3$ occlusion patterns: (i) right axis deviation, including deep $S_1$, not $Q_1$; (ii) *S-T* elevated slightly in Lead I; (iii) *S-T* depressed slightly in Lead III; (iv) $T_2$ and $T_3$ inverted or diphasic; (v) $R_1$ always marked; (vi) $T_1$ inverted.

Dr. Maddox went on to say that pericarditis was often missed clinically, but suspicions were aroused by the electrocardiogram. In the acute form it might complicate rheumatic and coronary heart disease, pneumonia, uræmia or heart wounds, producing a double effect on the electrocardiogram. Superficial myocarditis was always present. In the chronic form it might accompany tuberculosis, chronic constrictive pericarditis (Pick). Acute pericarditis had to be distinguished from coronary occlusion; the *S-T* segment was elevated in both, and low voltage occurred in both, but in acute pericarditis the *RS-T* segment was concave upwards. In pericardial effusion the *RS-T* elevation could occur in all standard leads. Isoelectric or inverted *T* waves, even of cove-plane type, could occur in both. In chronic pericarditis distinction might be difficult. The common changes were: (i) low voltage in the main leads, (ii) *T* wave inversion of "coronary type", (iii) frequent auricular fibrillation, (iv) long duration of these changes.

Referring to acute rheumatic carditis, Dr. Maddox said that 70% of the patients dying of the disease showed universal pericarditis. Very probably many of the cardiac deformities in acute rheumatism might be due to this cause. *T* wave inversion *et cetera* usually disappeared in five to fourteen weeks. Dr. Maddox, in conclusion, briefly discussed the changes resembling myocardial infarction produced by digitalis, quinidine and myxœdema.

### Arterio-Venous Aneurysm.

DR. J. H. HALLIDAY showed a male patient, aged twenty-nine years, the proprietor of a picture show. In 1925, at the age of thirteen years, he was accidentally shot through the lower part of the left thigh with a 0·32 revolver. The wound healed rapidly. In 1934 he noticed that the left leg was larger than the right and that some varicose veins had developed. This increase in size had been slowly progressive. His leg felt stiff after he had been sitting for any long period. He could play 36 holes of golf with ease. The patient had had rheumatic fever when he was aged six years; he was in bed for a "considerable time". He had pneumonia and pneumonic influenza when eight years old. His heart was thought to be affected when he was nineteen years of age.

Physical examination revealed a sparely built man, whose left leg was considerably larger than the right (one inch in the middle of the calf). Many varicose veins were present in the left leg, round the ankle of which many dilated venules gave a bluish discoloration. A pronounced thrill was felt beneath the bullet scar, and this could be traced proximally along the femoral and external iliac arteries as high as the umbilicus, and distally to the popliteal space. The femoral and external iliac arteries appeared to be considerably enlarged, with increased pulsation. Auscultation over the artery revealed a continuous murmur with systolic intensification; the maximum intensity corresponded to the area beneath the scar. The heart was enlarged and the apex beat was four and three-quarter inches to the left of the mid-line, in the fifth intercostal space. The sounds were clear and forcible. The systolic blood pressure was 154 and the diastolic pressure 70 millimetres of mercury; the diastolic level was ill defined, as the sound gradually disappeared towards zero. A skiagram of the heart revealed a greatly enlarged organ, both right and left ventricles being involved, and a definite pulmonary conus was present along the left border in the antero-posterior film. An electrocardiogram revealed pronounced right axis deviation.

Dr. Halliday remarked that this was a case of acquired arterio-venous aneurysm with typical physical signs. The cardiac problem was an interesting one, as it was complicated by the early history of rheumatism. However, there was no evidence of valvular disease, and the shape and size of the heart were consistent with that reported in other cases in association with arterio-venous aneurysm. It was intended to excise the aneurysm and to follow closely the effects on the cardio-vascular system. It was hoped that the heart would return to normal size.

### Occlusive Disease of the Femoral Artery.

Dr. Halliday's second patient was a foreman in a tobacco factory, where he had been employed for twenty-five years. He was aged forty-seven years. He inhaled the smoke of thirty cigarettes daily, and had always led an active life, with little or no ill health. In 1937, while playing tennis, he snapped the "monkey muscle" of his right leg, which subsequently became discoloured and bruised from knee to ankle. From that date he had had some discomfort across the ball of his right foot, particularly when taking exercise, though he continued playing tennis. During 1939 discomfort and numbness in the right foot increased, especially with effort. He consulted a chiropodist and had special shoes made, but obtained no relief. In December, 1939, he had an attack of "renal colic", and on resuming activity after two weeks in bed, found that slight walking exercise quickly produced severe cramping pain in the right calf. This disappeared quickly with rest. He returned to work in January, 1940, and a few days later, when jumping out of the way of a truck, felt "something go" at the back of his right knee; this was followed immediately by severe pain down the right leg, which persisted during the following night, and then gradually lessened. However, three nights after the occurrence he was awakened to find his leg and foot numb and dead, and on investigation he discovered that the foot was white and hard. This condition recurred each night and greatly interfered with his sleep.

Physical examination revealed a stout healthy man. There was no evidence of cardiac enlargement. The heart sounds were normal. The radial vessels were not palpable; the systolic blood pressure was 130 and the diastolic pressure 80 millimetres of mercury. No abnormality was discovered on examination of the central nervous system. Pronounced rubor of the right foot was noticeable when the limb was in the dependent position. On elevation the foot blanched rapidly. Equal pulsation of the femoral arteries was present in the femoral triangle, but no pulsation was present in the right popliteal artery; it was easily detected in the left. No pulsation could be detected in the right *dorsalis pedis* artery; it was present in the left.

Skiagrams of the heart and of the femoral arteries revealed no abnormalities. An arteriogram of the right femoral artery, with "Perabrodil", revealed a complete block of the femoral artery about three inches below the inguinal ligament. An electrocardiographic examination revealed no abnormality. The oscillometric index at the middle of the right leg was nil. On the left side it was two, at a pressure of 130 millimetres of mercury. A test was made of the capacity for vasodilatation of the lower extremities, by means of heat applied to the arms; the skin temperatures were recorded by the "Dermatherm". The room temperature was 21° C. and the mouth temperature was 36·5° C. (97·8° F.). The skin temperature was recorded after exposure of the lower limbs for half an hour to room temperature; the patient was at rest in bed. The mean of three readings was taken. The temperature of the right great toe was 23·5° C. and that of the left great toe was 22° C. The skin and mouth temperatures were recorded after immersion of both arms in water for thirty-five minutes at 45° C. The mouth temperature was 37·4° C. (99·4° F.); that of the right great toe was 25° C. and that of the left great toe was 29° C.

Intradermal injections of 0·1 cubic centimetre of histamine (1 in 1,000) produced satisfactory flares on each foot and shin. There was no response to the Wassermann test.

After a period of rest in bed, with daily hot arm baths and Buerger's exercises and mild sedatives, the patient returned to work. Elevation of the head of his bed about six inches had greatly lessened the numbness in his foot at night and had allowed satisfactory sleep. He was able to walk half a mile quietly with no discomfort. He had ceased smoking and was meticulous in the care of his feet.

Dr. Halliday said that this was a case of occlusive disease of the right femoral artery, the ætiology of which was uncertain. It might have some connexion with the original injury at tennis, which might have been vascular rather than muscular. *Thrombo-angiitis obliterans* could not be excluded, and the patient's occupation might be significant in that regard. Boyd had recently described cases associated with primary intraarterial thrombosis and no venous involvement, and had differentiated a proximal type in which the main triad of symptoms were: (i) intermittent claudication of the calf muscles; (ii) pronounced postural colour changes in the limb; (iii) absence of pulsation in the larger vessels. These comprised the main features of the case under discussion. There was no evidence to support an arteriosclerotic origin.

### Occlusive Peripheral Vascular Disease.

Dr. Halliday finally showed a male patient, aged forty-three years, a commercial traveller by occupation. In 1937 pain developed in the region of the right ankle and calf; this occurred after walking and ceased with rest. It was followed in a few months' time by the development of similar symptoms in the left leg. This pain had gradually been provoked with less and less effort, and now after walking 200 yards the patient was compelled to stop on account of the severity of the pain. After five minutes' rest he was able to walk a similar distance. He had not noticed any changes in colour in the extremities. He first presented himself at the orthopædic department of the hospital in January, 1940, and was subsequently transferred to the medical out-patient department. He had also suffered from chronic dyspeptic symptoms for ten years. He did not drink and was a light smoker. In February, 1940, he was suddenly awakened by an attack of extreme breathlessness, associated with tightness in his chest, and became very giddy. He remained in bed next day, and after a second similar attack he was seen by a doctor, who gave him a hypodermic injection and admitted him at once to hospital, where he remained for three weeks. Since this attack he had noticed that the pain in his legs occurred after very slight exertion.

Physical examination revealed a florid man, with a palpable radial artery. The systolic blood pressure was 160 and the diastolic pressure 110 millimetres of mercury. Pulsation was present in both femoral triangles, but no pulsation could be discovered in the popliteal artery on either side, or in the distal branches. No trophic or colour changes could be seen on the skin of either of the lower extremities. Serial electrocardiograms taken during March, 1940, revealed progressive changes in intraventricular conduction, consistent with posterior infarction. Skiagrams of the aorta and femoral arteries revealed atheromatous plaques. Oscillometric readings on both calves resulted in a maximum index of 0·5 on both sides, at a pressure of 110 millimetres of mercury. Injections of 0·1 cubic centimetre of 1 in 1,000 histamine produced satisfactory flares after five minutes on the dorsum of each foot and shin, and on the lower third of the thigh. There were no abnormal signs in the central nervous system, and the blood serum did not react to the Wassermann test.

Dr. Halliday remarked that the patient's illness was an example of occlusive peripheral vascular disease, due to atherosclerosis in association with coronary thrombosis in a man in early middle age.

### Dermoid Cyst of the Mediastinum.

DR. B. T. EDYE showed a female patient, aged twenty-five years, who had been admitted to hospital on November 10, 1939. In 1937, while living in Tamworth, the patient had an attack of "pleurisy" at the base of the right lung and was in hospital for ten days; after returning home she coughed up a small amount of blood-stained sputum. Otherwise she had had no cough, sputum or hæmoptysis. In May, 1939, she had an attack of a "smothering" sensation and breathlessness, which lasted for ten days and was diagnosed as "asthma". Six weeks prior to the meeting pain began in the axillary region on each side, but more on the left side; the pain was intermittent and shooting in nature, though not severe. The patient had lost seven pounds in weight in six weeks. She had lived in Tamworth until two years prior to the meeting and worked on a farm. Her father had hydatid disease of the lung.

On examination the patient appeared well and comfortable. Her pulse rate was 70 per minute, the systolic blood pressure was 120 and the diastolic pressure 80 millimetres of mercury. The heart sounds were normal and the apex beat was not displaced. The lungs were clear. The Wassermann and Kline tests produced no reactions. The Casoni test and the complement fixation test for hydatid disease produced reactions; a differential leucocyte count showed that 4% were eosinophile cells.

Radiological examination of the chest revealed a tumour in the anterior portion of the mediastinum, closely applied to the right side of the heart. A diagnosis of mediastinal dermoid or hydatid cyst was made.

At operation on November 28, 1939, a section, three inches long, of the anterior end of the fifth right rib, together with its corresponding cartilage was excised, iodoform gauze was packed onto the pleura and the wound was sutured. After the operation a right pleural effusion and pneumothorax developed, but the wound healed aseptically. At a second operation on December 12, 1939, the wound was reopened, the gauze was removed and fluid was aspirated from the pleural cavity. The tumour was exposed and proved to be cystic. It was emptied of creamy sebaceous material, in which hairs were suspended. The wall was dissected from the adjacent structure to which it was firmly adherent. The wound was closed without drainage after inflation of the lung. During recovery there was evidence of some pleural effusion; but this gradually disappeared, and the patient, when discharged from hospital on January 18, 1940, was very well.

Dr. G. Davies, in his pathological report on the cyst, stated that macroscopic examination of the cyst wall showed it to be lined by wrinkled epithelium in which there were many hairs. Some of these sprang from a white nodule. Microscopic examination gave the following results. One of the sections was covered on one side by stratified squamous epithelium, deep to which were hair follicles and sebaceous glands embedded in fibrous and fatty tissue. Examination of another section revealed a very similar structure; but in the deeper parts there were some glandular acini in ducts gathered together in lobules. These somewhat resembled pancreatic tissue. In a third section there was similar tissue, which was very fibrous and in parts was associated with structures resembling islets of Langerhans. In this section some of the superficial epithelium was of the squamous type, but part resembled respiratory epithelium, being pseudo-stratified, ciliated and columnar.

### Intrathoracic Goitre.

Dr. Edye's second patient was a male, aged fifty-five years, who had been admitted to hospital on December 1, 1939. For three years he had had an irregular enlargement of the thyreoid gland, and for the last three months he had been suffering from severe dyspnœa so that the slightest exertion caused breathlessness, and he was unable to lie down. He had had a spasmodic cough and his voice had been hoarse.

Examination revealed an irregular enlargement of the thyreoid gland, typical of multiple adenomata, and dilatation of the superficial veins of the neck and thorax, but no signs of thyreotoxicosis. The pulse rate varied from 80 to 90 per minute; the systolic blood pressure was 170 and the diastolic pressure was 113 millimetres of mercury. The breath sounds were diminished and there was a very distinct asthmatic wheeze. Both the Wassermann and Kline tests produced reactions. Radiological examination of the chest demonstrated a large mass in the superior part of the mediastinum, compressing the trachea and displacing it to the left.

At operation on December 22, 1939, the thyreoid gland was exposed by the usual incision, and after division of the right depressor muscles subtotal thyreoidectomy was performed; the blood supply was thus controlled and a large intrathoracic extension on the right side was dislodged without difficulty. Recovery was uneventful. The tumour consisted of multiple colloid adenomata.

Dr. Edye showed another patient suffering from intrathoracic goitre. She was aged forty-seven years, and had been admitted to hospital on December 4, 1939. For the past twelve months the patient had noticed increasing difficulty in breathing, especially on exertion, and finally she had to cease work. She had had an enlargement of the thyreoid gland for thirteen years. Six weeks prior to the meeting she had an attack of vomiting associated with breathlessness and dizziness. Her weight had increased and her feet swelled after standing or walking. She had had ten children.

On examination considerable irregular enlargement of the thyreoid gland was noted, especially on the left side. There were no signs of thyreotoxicosis. The pulse rate varied from 70 to 84 beats per minute. The systolic blood pressure was 160 and the diastolic pressure was 110 millimetres of mercury. The basal metabolic rate was −13%. A radio-

logical examination of the chest revealed an intrathoracic extension of the thyreoid gland.

At operation on December 19, 1939, subtotal thyreoidectomy was performed and an intrathoracic extension on the left side was dislodged. Convalescence was uneventful. The tumour consisted of multiple colloid adenomata.

### Hydatid Cyst of the Kidney.

Dr. Edye finally showed a male patient, aged forty-eight years, suffering from a hydatid cyst of the kidney. In 1927 his appendix had been removed, following an acute attack of pain in the right loin and right iliac region. A week after leaving hospital he had a similar attack of pain and passed hydatid material in the urine. The passage of hydatid cysts and membrane had occurred at intervals since, sometimes with and sometimes without pain. In the past six months he had had two severe attacks of pain, which were referred more to the right side of the hypochondrium than to any other area. The patient had always lived out west and was a farmer. No tumour was palpable in the renal regions. At the time of the meeting the urine was clear. Graham's test revealed a normal gall-bladder. Serological tests for hydatids produced positive reactions. The patient was awaiting admission to hospital for operation.

### Plastic Surgery.

DR. JOHN S. MACMAHON showed the results of a series of plastic operations. His first patient, a male, aged seventeen years, had met with an accident on March 3, 1939, his left hand being extensively crushed in a roller. His second, third, fourth and fifth fingers were pulped. The whole of the skin of the palm of the hand was missing, together with the skin from the distal half of the dorsum of the hand. There was a compound fracture of the middle phalanx of the thumb. At operation the fingers were trimmed through the bases of the proximal phalanges, and the hand was dressed with "Vaseline" gauze.

On April 5 a tube graft, which was later attached to the dorsum of the hand, was made on the right side of the thorax. On April 28 the tube was opened out, wrapped round the bases of the fingers, and sutured to the margins of the wound of the palm. Infection occurred in the fat and half of the tube graft was lost. The palm of the hand was then covered by means of a Thiersch graft and the patient was discharged from hospital.

He was readmitted on June 12 with pronounced contracture of the palm of the hand and very little movement in the thumb, which was fixed to the palm by scar tissue. A further tube graft was made on the left thigh on September 7. Three weeks later the scar tissue was removed from the palm of the hand and one end of the tube graft was attached. One month later, on October 19, the tube was detached from the thigh and opened out on the hand.

At the time of the meeting the patient had a useful hand; the palm was covered with skin and fat and sensation was returning. He had a full range of movement of the thumb and had quite a firm grip, as he was able to approximate the thumb against the covered stumps of the second, third, fourth and fifth fingers.

Dr. MacMahon's second patient, a female, aged seventeen years, had developed a frog-neck following a burn. Extensive keloid contracture extended from over the sternum up to the lower border of the mandible. The chin was drawn downwards and extension of the head was rendered impossible. The angles of the mouth and the lower lip were also drawn downwards; this gave her a jowled expression.

On April 13, 1939, a tube graft, conical in shape, was made on the lateral aspect of the right breast. This was later transferred to the neck, the submental region and scar tissue having been excised along the line of the mandible and the submental region freed. On August 11 a large tube graft, four inches in width and eight inches long, was made from the region of the left loin. Four weeks later this was attached to the forearm and carried up to the region of the neck to replace the scar tissue on the front and lateral aspects of the neck.

At the time of the meeting the patient had a well-formed submental region and front of the neck, and was able to hyperextend her neck over a normal range. The lower lip and angles of her mouth had regained their normal contour and her expression was totally different, the jowled expression having gone.

Dr. MacMahon's third patient, a female, aged sixty-two years, had had a partial rhinoplasty performed on October 12, 1938, for a radionecrotic ulcer which extended in a saddle-shaped fashion across the nose from just above the tip upwards for one inch; the nasal cavities were exposed. An inner lining was formed from septal mucosa and a pedicled flap was turned down from the forehead; the unused portion was replaced at a later date. At the time of the meeting the transplanted area of skin was normally pigmented and could only with difficulty be recognized from the surrounding skin. The scarring on the forehead as a result of the flap was not very noticeable, being artistically hidden by the arrangement of the patient's hair.

Dr. MacMahon's next patient, a female, aged seventeen years, had met with an accident ten years earlier, in which she had sustained a lacerated wound of the nose with considerable depression of the bridge; this gave her the appearance of a congenital syphilitic. In 1933 a cartilage graft operation was carried out at the Royal Alexandra Hospital for Children, but the graft was absorbed. She had a second operation in 1936 with only slight improvement. On February 13, 1940, a cartilage graft operation was performed after the method of Sir Harold Gillies. The cartilage was notched and hinged, the longer portion extending upwards to the frontal bone between the eyes, and the shorter portion extending backwards as a maxillary peg.

Dr. MacMahon then showed two patients who had undergone excision of a large epithelioma of the dorsum of the hand; skin grafts had replaced the lost tissue. In one case a full thickness graft was performed, and in the other a thick Thiersch graft. Dr. MacMahon said that a thick Thiersch graft gave the same result as a full thickness graft. In the cases in question the skin was movable over the deeper tissues. There was no interference with function and the hands were practically normal in appearance.

Dr. MacMahon finally showed a male patient, aged fifty years. Destruction of the lower lip by malignant disease had been treated by insertion of radium needles on February 8, 1929. The tumour recurred, and excision of the lower lip was carried out on January 14, 1931. On January 1, 1935, the patient was admitted to hospital for plastic reconstruction of the lower lip, as he had no control of his saliva, which continually drooled from his mouth. This was carried out by transplantation of a tube graft formed on the side of the neck. The patient was able to retain his saliva and wore a lower denture without inconvenience. The patient had a rather ruddy complexion, and the transplanted skin had taken on the same hue from exposure.

### Ruptured Bladder and Fractured Pelvis.

DR. F. W. NIESCHE showed a female patient, aged eighteen years, who had been thrown off a motor cycle. On her admission to hospital on February 4, 1940, she was suffering from numerous abrasions on the extremities and face, obvious dislocation of the left wrist and shock. She complained of severe pain across the lower portion of the abdomen, and had pronounced muscle guarding and tenderness in this region. She was unable to flex the legs in the dorsal position. A small amount of blood was escaping from the urethra; some urine, but mostly bright blood, was withdrawn on catheterization. Her condition was diagnosed as a ruptured bladder. X-ray films revealed dislocation of the left wrist, but no fracture. The pelvis was fractured in three places—both the superior and the inferior ramus on the right side and the superior ramus on the left; the symphysis was separated and the fragments had been driven inwards. At operation the pelvic fragments were reduced by manipulation through the vagina. A subumbilical median incision was made through the abdominal wall, and some urine and much blood were found in the cave of Retzius and extending into the anterior abdominal wall. Two perforations were found in the anterior wall of the bladder; the more accessible tear was enlarged and the interior of the bladder was examined. It was found easier to repair the second tear from inside the bladder. The peritoneal cavity was opened to make certain that there was no intraperitoneal wound in the bladder wall, and then the peritoneum was immediately sutured. The first tear in the bladder wall was approximated round a rubber tube, which was brought out through the abdominal wall. A small tube was inserted behind the symphysis to drain the cave of Retzius. The dislocation of the wrist was reduced and the limb was put up in plaster. A pelvic sling was applied.

Subsequent X-ray examination revealed the fractured pelvis in good position. On February 20, 1940, the suprapubic tube was removed from the bladder and a catheter was inserted through the urethra. On March 2, 1940, the wound was healed and the catheter was removed. The patient's convalescence was interrupted by two attacks of pyrexia due to acute pyelitis; this was easily controlled by means of "M & B 693". She was discharged from hospital, well, on April 22, 1940. At the time of the meeting she was very well, with no pelvic deformity or disability.

### Compound Fracture of the Metacarpal Bones.

Dr. Niesche's second patient was a male, aged twenty-five years; on January 18, 1940, his right hand had been crushed

in a metal press whilst he was at work. There was a lacerated wound on the dorsum of the right hand, extending across four metacarpal bones. Bones were exposed. There were compound fractures of the second, third, fourth and fifth metacarpal bones. No gross nerve injury was detected on clinical examination. The extensor tendons were not completely severed, but were much stretched. The terminal phalanx of the thumb was hanging by palmar skin and the long flexor tendon.

An X-ray examination revealed transverse fractures of the second, third, fourth and fifth metacarpal bones about their distal thirds and with half an inch overlapping. At operation the lacerations were excised, cleaned and sutured. The lateral extensor tendon for the index finger was sutured. The viability of the terminal portion of the thumb was doubtful. The thumb was repaired and the extensor tendon was sutured. Böhler's extension finger splints were applied to all four metacarpal bones with wire traction through the finger tips, and the hand and forearm were put up in a plaster splint, the thumb being included.

On January 24, 1940, the plaster splint was removed and the bones were reset; a plaster cast and splints were reapplied. On February 25, 1940, an X-ray examination revealed satisfactory alignment of the second and fourth metacarpals, with union taking place. On February 28, 1940, an operation was performed for open reduction of the fractures of the third and fifth metacarpal bones and reapplication of the plaster splint without extension. On March 4, 1940, an X-ray examination showed that all the fragments were in good position. Subsequently the plaster splint was removed and the patient had massage with an increasing range of movement. A small sequestrum had to be removed from the terminal phalanx of the thumb, adjacent to the joint. At the time of the meeting the range of movement was very satisfactory.

### Compound Comminuted Fractures of the Tibia and Fibula in their Upper Extremities.

Dr. Niesche's next patient was a male, aged thirty-five years. On October 13, 1939, a portion of a revolving machine had come loose and struck the patient with great force on the left leg. On examination very extensive comminuted fractures of the tibia and fibula in their upper extremities were found, with a large wound over the upper part of the tibia; the fractures were both compound and comminuted. An X-ray examination revealed an extensively comminuted fracture of the upper end of the tibia, the bone being broken into numerous fragments. There was also a fracture of the fibula at the same level.

At operation the wound was excised and sutured, the fractures were set in a Böhler's screw traction frame with a pin through the calcaneus, and a plaster cast was applied extending from the toes to the upper portion of the thigh, incorporating the pin in the plaster. A window was cut in the plaster cast and a small rubber drain was left in the corner of the wound. An X-ray film showed that the position of the fragments was fairly satisfactory. On January 3, 1940, the plaster cast was becoming loose and foul, and it was removed. The wound, which had partly broken down, was dressed with "Vaseline" gauze; the plaster cast was reapplied with no window and the pin was removed. On February 7, 1940, the plaster cast was removed; the wound was healed. A full-length plaster cast was applied. An X-ray examination revealed a small amount of callus. A walking iron was applied. The plaster cast was subsequently removed and an Unna's paste bandage was applied. By May 21, 1940, the patient was having massage; he was walking with a stick and had an increasing range of movement in his knee joint.

### High Ligation and Injection of Varicose Veins.

Dr. N. R. Wyndham demonstrated on a male patient high ligation of the saphenous vein and injection of sclerosing fluids. Dr. Wyndham said that the fluid used in the majority of cases was a 10% solution of sodium ricinoleate. A few patients had been treated with a 5% solution of sodium morrhuate. No patients had been confined to bed, ambulatory treatment being essential. The patients continued their usual occupations the following day. Severe reactions were sometimes experienced, but never complained about by the patients. Clinical tests were said to be necessary prior to the inception of treatment, to demonstrate the patency of the deep communicating veins of the leg and the absence of varicosity in these veins. A history of deep thrombosis did not prevent the use of this treatment, provided that these criteria were fulfilled.

*(To be continued.)*

# The Royal Australasian College of Physicians.

## MEETING AT SYDNEY.

A meeting of the Royal Australasian College of Physicians was held in Sydney on Friday and Saturday, September 6 and 7, 1940. Visiting Fellows and Members of the College came from Queensland, Victoria, South Australia, Tasmania and New Zealand.

The Council of the College met on the morning of Friday, September 6. Those present were the President (Dr. S. V. Sewell), Sir Charles Blackburn, Dr. S. O. Cowen, Dr. C. T. Champion de Crespigny, Dr. J. G. Hayden, Dr. Konrad Hiller, Dr. A. W. Holmes à Court, Dr. L. S. Latham, Dr. C. G. McDonald, Dr. Alex P. Murphy, Dr. M. D. Silberberg, Dr. S. A. Smith, Dr. A. H. Tebbutt and Dr. A. E. Rowden White. Nine new Members, who had satisfied the Board of Censors at the examination which preceded the meeting, were admitted to membership by the President.

A luncheon for Fellows and Members was held on Friday, September 6, at the Carlton Hotel. This was the only official gathering of a social nature held during the meeting.

At an extraordinary general meeting of the College held in the Stawell Hall after the luncheon, four gentlemen were elected to fellowship under article 40 of the constitution. These were Dr. F. B. Byrom, of New South Wales, Dr. N. H. Fairley, of Victoria, Professor F. H. Smirk, of New Zealand, and Professor R. D. Wright, of Victoria. Dr. Byrom was admitted to fellowship in person by the President.

The first scientific session was held after the general meeting. The programme was as follows: "The Effect of Experimental Hypertension on the Kidney", Dr. F. B. Byrom; "Constrictive Pericarditis: Report of a Case", by Dr. J. H. Halliday; and "Report of a Case of Addison's Disease treated by Implantation of Tablets of Desoxycorticosterone Acetate", by Dr. Alex P. Murphy.

On the evening of Friday, September 6, a joint scientific session of the Royal Australasian College of Physicians and the Royal Australasian College of Surgeons was held, the subject being "Post-Operative Thrombosis and Embolism". Dr. J. G. Hayden, F.R.A.C.P., and Mr. Balcombe Quick, F.R.A.C.S., opened the discussion on the respective medical and surgical aspects of these complications. Dr. A. J. Hood Stobo described the electrocardiographic changes characteristic of pulmonary embolism. A general discussion followed.

On the morning of Saturday, September 7, the Royal Australasian College of Physicians held its second scientific session, the programme including addresses by Professor H. Priestley on "Irrational Medical Practice", and by Dr. N. W. Markwell on "A Military Psychohygienic Section". A general discussion on the prevention of war neuroses followed Dr. Markwell's contribution.

The President and Council of the Royal Australasian College of Physicians entertained the President and Council of the Royal Australasian College of Surgeons at luncheon at the Union Club after the morning meeting. A joint meeting of the councils of the two colleges held in the afternoon concluded the programme.

# Obituary.

## EDWARD JOHNSTONE JENKINS.

We are indebted to Dr. R. Scot Skirving for the following appreciation of the late Dr. Edward Johnstone Jenkins.

To the older generation of medical men in Australia the death of Edward Johnstone Jenkins will be felt as a personal sorrow and a loss to our profession, which he certainly did adorn, both in character as a man and as a cultured and learned physician.

*De mortuis nil nisi bonum*, is, no doubt, an excellent saying, but at times I find it a hard one; it is not so here, for it would be hard indeed to find anything to write about Jenkins which was not good. His father was Dr. R. L. Jenkins, who came to New South Wales perhaps nearly one hundred years ago and prospered, first as a medical man, then later as a pastoralist and breeder of blood stock. At his home, "Nepean Towers", there existed, naturally and not as an exotic, something of the atmosphere of England, of our now sorely tried Homeland, like that of a country house in a Kent or Sussex setting. In that quiet home the writer of this article remembers with affection the kindness

and welcome he, a young stranger in a strange land, received from the mother and family of his friend. I think he was born at Tamworth in 1855, and, as a small boy, went to Macquarie Fields School, where Dr. William Chisholm, who is still with us, was a fellow pupil. Then he, when that school was amalgamated with The King's School at Parramatta, went with it and in 1872 became its captain and Broughton scholar and held two other distinctions; so he quite early showed his intellectual ability.

About 1874 he went to Oxford—to Trinity, where two other New South Welshmen were students—Consett Stephen and B. R. Wise. He graduated in the honours school of natural science and then proceeded to Saint Bartholomew's Hospital to study medicine. Later on he passed his M.R.C.P. examination and in after years received the Fellowship of the College.

He held the usual resident posts at Bart.'s, and had Gee, Church, Savory and Mathew Duncan as his chiefs. The Paget tradition coloured his outlook in many ways. He finally returned to Sydney in 1883, after about ten years' absence spent in successful study, with an arts and a medical degree from Oxford and, as said, the Membership of the Royal College of Physicians of London. He was then equipped with the hall-mark of learning more highly, both in culture and medicine, than, I think, any other doctor in the colony (I only remember two men who were Fellows at this time of the Royal College of Surgeons, and not one who held a higher qualification in medicine). Almost at once he was appointed resident medical officer at the new Prince Alfred Hospital. It was there I had the luck to meet him and begin a life-long friendship. Truly a happy meeting for me, for I soon discovered that he had a quite delightful personality and was a really admirable and learned young doctor. Time passed, and Jenkins succeeded to the medical superintendency of the Prince Alfred Hospital. When, later, he resigned and began private practice in Macquarie Street, I think that there could have been few men better qualified professionally and in general culture to rise to the top of the tree.

It so happened about this time that an assistant-physiciancy at the Sydney Hospital became vacant. Jenkins applied, was appointed, and so Prince Alfred Hospital lost him to the honorary staff of the senior institution. He was also soon given a physiciancy on the staff of the Sick Children's Hospital. He remained on the active staff of the Sydney Hospital till 1914. During all these years he taught clinical medicine, and taught it well. I am told by some of his pupils that he was at his best, not in lecturing formally to a class, but rather in giving patient personal instruction to a few, at the bedside, and there he really excelled. I myself saw much of his work and learned to trust in the sanity and wisdom of his methods and conclusions. I say here, as I have often said in the past, that two men in my time, in Sydney, stood out as masters in the art of clinical examination; one of these was Charles Dagnall Clark, who practised many years ago at North Sydney, and the other was Edward Jenkins.

I think the mantle of Gee and Church fell fully on his shoulders in the way he went about his work at the bedside. In due season he was made President of the British Medical Association in New South Wales and was on the Medical Board for a long time.

It is only in quite recent times that the giving of anæsthetics has crystallized, more or less, into a water-tight specialty in perhaps less than half a dozen big cities in Australia. In earlier years, of course, everyone and anyone was likely to administer anæsthetics if asked. No doubt accidents did sometimes happen, when cases which now are known to need all sorts of care and forethought were operated upon with the valour of ignorance and with often a debauch of chloroform or ether. But all the same, certain men, without the modern, quite righteous, elaborate pre-medication, scientific dosage and other safeguards, gave anæsthetics daily with skill, care and wonderful safety and success. Some young men, in the leaner years before much practice, consulting or otherwise, came to them, filled in their time and rounded off their slender incomes by giving chloroform or ether, while waiting till the more succulent morsels of regular practice fell into their expectant laps. This practice in those days was quite proper and natural, and of the men who were especially safe so doing was Jenkins. But Jenkins kept on giving anæsthetics for far too long a period—I think it narrowed his career as a consultant physician.

Jenkins's equanimity of temper and habit of forgiveness of wrong and rudeness were at times my admiration, but sometimes the reverse, for he tried always to excuse people when it would have perhaps been better to have taken them to task. As another colleague of mine, a famous man, and a good one, used to say to me: "Yes! Yes! Let us forgive our enemies but not forget them."

I always looked on Jenkins as having a finely balanced education. He was no mean classical scholar, an accomplishment common enough when Latin and Greek were the essentials of the proper education of a consulting physician, a possession rare, and getting more rare, in these days when Latin and Greek are no longer compulsory subjects for a university degree in medicine. I have seen him, with envy in my heart, revelling in classical authors, savouring their beauties, just as I, with regrettably less learning, might comfort my soul with some stately passage from Gibbon or a Conrad's mozaic of delightful English. Apart from general literature and a passion for poetry which were intellectual hobbies, I think he liked cricket best of games. His country upbringing made him at home on a horse's back, and I certainly remember him as a first-rate shot—probably he could use a rifle equally well. He deeply enjoyed flowers and birds, and indeed all sorts of natural history things. In the early days of practice, he, MacCormick, Huxtable and I, and probably others whom I forget, used to rise early on summer mornings and walk through the botanical gardens to the swimming baths, and as we went Jenkins used to roll off the botanical names of heaps of the plants, to our no small joy. Oh, he was a taking lad, and it was impossible to be quite

one's own unpleasant self with him as a corrective! It is true that his end happily came suddenly with "indemnifying swiftness" while sitting at his desk; but one must remember that he endured a number of years of failing health in which work and play were equally difficult and distressing. When the heart begins to give out and signs and symptoms of its inexorable decay are present daily, when the cardiac muscle has no reserve of capital and each systole is a hand-to-mouth necessity, life cannot be very pleasant, and it is difficult to be patient and uncomplaining; but Jenkins was so to a remarkable degree. I never heard an impatient word or saw a peevish gesture escape him in those last years of weakness. Dr. Norman Dunlop one day said to me under very similar conditions: "It is not difficult to be brave and patient for short periods of acute distress or pain; but how is one to show a *'mens æqua rebus in arduis'* if it goes on indefinitely for months? For short periods my head may be 'bloody but unbowed'; but for long stretches of suffering how shall one continue to play the man?" But both of these fine fellows preeminently did do so.

I hope I have made the readers of this appreciation realize that he who has gone from us was a doctor of the best ability, learning and wisdom. I hope, too, that I have succeeded in sketching a man who in the material worldly environment of daily life remained unspoiled, unselfish and justly beloved. This is high praise, but every bit of it is true and justified. I dislike the hackneyed phrase, but I am almost forced to say that he was indeed "a beloved physician".

Our profession is the poorer by his passing—he, I suppose, belonged in manner, education and spirit to a mellower age, which has gone never to return; but the old-world fragrance of his ways, his patience and courage in all the various trials he met with were a daily lesson on conduct of life to those who saw and admired, and, let us hope, sometimes profited by his example. I think today that many old patients, many old friends, and, above all, those who have specially benefited by his skill and sympathy, must be expressing their inmost feelings by repeating to themselves the third verse of the first chapter of the epistle of Paul to the Philippians.

RONALD PARKER SMITH.

WE regret to announce the death of Dr. Ronald Parker Smith, which occurred on October 8, 1940, at Sydney, New South Wales.

## Correspondence.

### THE RELEASE OF FIXED "RECORD" SYRINGES.

SIR: I offer a suggestion for treatment of a "Record" syringe the plunger of which has become fixed. Place the syringe in the refrigerator for a wee while and the relative coefficients of contraction will render the piston mobile.

Yours, etc.,

A. K. GAULT.

178, North Terrace,
Adelaide,
October 7, 1940.

## Australian Medical Board Proceedings.

### TASMANIA.

THE undermentioned has been registered, pursuant to the provisions of the *Medical Act*, 1918, of Tasmania, as a duly qualified medical practitioner:

Phillips, Frank, M.R.C.S. (England), L.R.C.P. (London), 1928, D.O.M.S. (London), 1930, D.L.O. (London), 1930, D.O. (Oxon), 1930, Hobart.

## Nominations and Elections.

THE undermentioned have been elected members of the New South Wales Branch of the British Medical Association:

Condon, Richard Daniel, M.B., B.S., 1939 (Univ. Sydney), Main Road, Scarborough.

Cranna, Max Maziere, M.B., B.S., 1939 (Univ. Sydney), 363, Rocky Point Road, Ramsgate.

Engisch, Herbert John Charles, M.B., B.S., 1939 (Univ. Sydney), Springwood Road, Springwood.

Robertson, Sandy Edwin John, M.B., B.S., 1939 (Univ. Sydney), 114, Birriga Road, Bellevue Hill.

## Books Received.

"Turkish Days and Ways", by J. Brown, B.A., M.D., D.P.H.; 1940. Australia: Angus and Robertson Limited. Crown 8vo, pp. 288. Price: 6s. net.

"Advice to the Expectant Mother on the Care of her Health and that of her Child", by F. J. Browne, M.D., D.Sc., F.R.C.S.E., F.R.C.O.G.; Fifth Edition; 1940. Edinburgh: E. and S. Livingstone. Crown 8vo, pp. 48. Price: 6d. net.

## Diary for the Month.

OCT. 22.—New South Wales Branch, B.M.A.: Medical Politics Committee.
OCT. 23.—Victorian Branch, B.M.A.: Council.
OCT. 24.—New South Wales Branch, B.M.A.: Clinical.
OCT. 25.—Tasmanian Branch, B.M.A.: Council.
OCT. 25.—Queensland Branch, B.M.A.: Council.
OCT. 31.—New South Wales Branch, B.M.A.: Branch.
NOV. 1.—Queensland Branch, B.M.A.: Branch.
NOV. 5.—New South Wales Branch, B.M.A.: Organization and Science Committee.
NOV. 6.—Western Australian Branch, B.M.A.: Council.
NOV. 6.—Victorian Branch, B.M.A.: Branch.
NOV. 7.—South Australian Branch, B.M.A.: Council.
NOV. 8.—Queensland Branch, B.M.A.: Council.
NOV. 12.—Tasmanian Branch, B.M.A.: Branch.
NOV. 12.—New South Wales Branch, B.M.A.: Executive and Finance Committee.

## Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

*New South Wales Branch* (Honorary Secretary, 135, Macquarie Street, Sydney): Australian Natives' Association; Ashfield and District United Friendly Societies' Dispensary; Balmain United Friendly Societies' Dispensary; Leichhardt and Petersham United Friendly Societies' Dispensary; Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney; North Sydney Friendly Societies' Dispensary Limited; People's Prudential Assurance Company Limited; Phœnix Mutual Provident Society.

*Victorian Branch* (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federated Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

*Queensland Branch* (Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17): Brisbane Associated Friendly Societies' Medical Institute; Proserpine District Hospital. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

*South Australian Branch* (Honorary Secretary, 178, North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

*Western Australian Branch* (Honorary Secretary, 205, Saint George's Terrace, Perth): Wiluna Hospital; all Contract Practice appointments in Western Australia.

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